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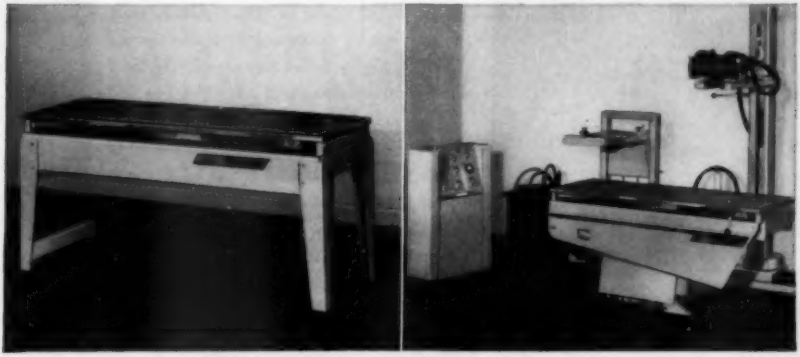

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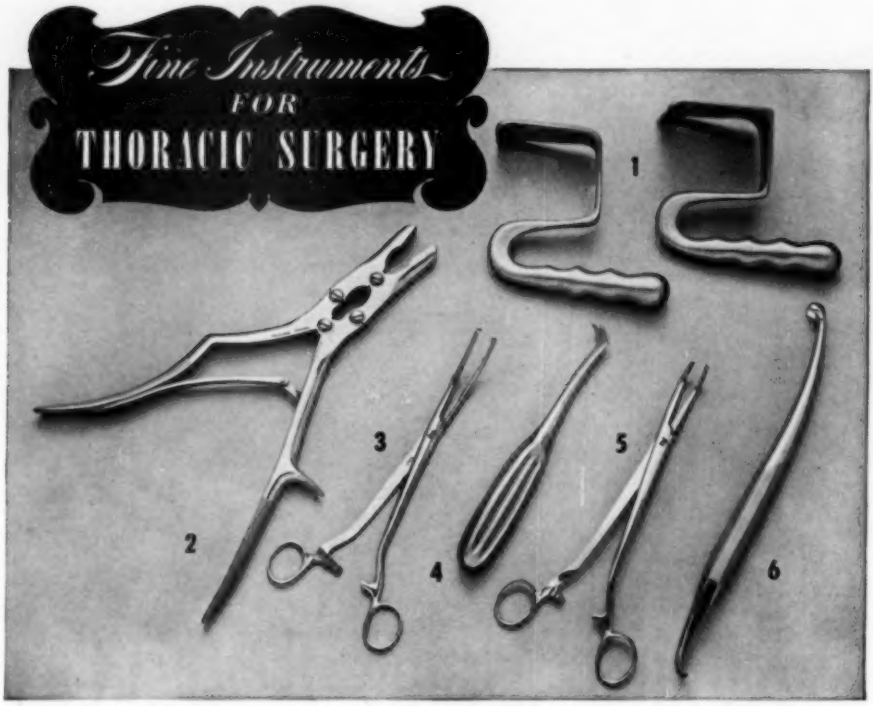

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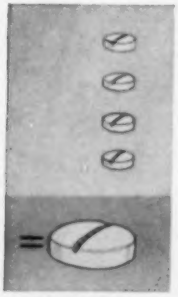

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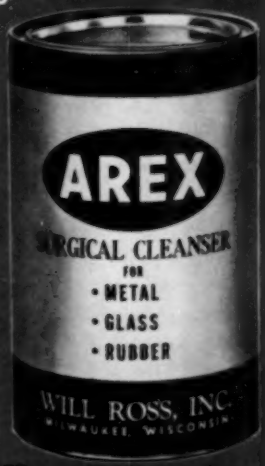

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In Volume 63, No. 1, 1951, "Antimicrobial Activity of *Streptomyces Floridae* and of Viomycin", Table 2, footnote * should read "Isolate No. A5014" instead of "Isolate No. A5104.

PULMONARY FUNCTION FOLLOWING DECORTICATION OF THE LUNG[1, 2]

DOUGLAS CARROLL, JOHN McCLEMENT,[3] AARON HIMMELSTEIN, AND ANDRE COURNAND

(Received for publication October 3, 1950)

INTRODUCTION

Although decortication of the lung has been widely used for removing thickened pleura and expanding incarcerated lungs, few studies of the physiological effects of this operation have been reported (1, 2). Gordon and Welles (1) have reported such studies performed on patients who had decortications for tuberculous pleural disease. Although the procedure was generally successful clinically, especially when combined with thoracoplasty, there was no significant increase in the pulmonary function. The writers noted that the results of decortication in these tuberculous cases were not as satisfactory as the results obtained in one case of hemothorax reported by Wright and his associates (2).

Studies on 2 additional patients who had decortications have been published (2). In a patient with chronic traumatic hemothorax, prior to operation there was a reduction in the lung volumes and maximum breathing capacity. Bronchospirometry demonstrated ventilation of poorly perfused areas of the lung on the side of the hemothorax. Exertional dyspnea developed at a low work level. Following decortication there was improvement in all measurements, with return to the normal predicted values. A second patient with a spontaneous hemopneumothorax, possibly complicated by empyema, was studied after decortication. The lung volumes and maximum breathing capacity (MBC) were normal, and the oxygen saturation of the arterial blood was reduced during exercise. It was suggested that perfusion of poorly ventilated alveoli persisted.

In these few studies of pulmonary function after decortication, the type of case is not representative of all the physiological problems related to this operation. For instance, the only cases of hemothorax reported were in patients who were treated with decortication within a relatively short time after the onset of the hemothorax. Furthermore, all but one of the reported tuberculous patients had been treated previously with pneumothorax; all had underlying lung disease and were treated with thoracoplasty in addition to decortication. For these reasons, the effect of decortication upon pulmonary function cannot be evaluated completely until more data are available.

The purpose of this report is to extend the observations already made on pul-

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[2] The work described in this paper was supported by grants from the Commonwealth Fund.

[3] James Alexander Miller Research Fellow.

monary function after decortication, and to help evaluate more completely the place of decortication in nontuberculous and tuberculous pleural disease. Because this procedure may occasionally be combined with thoracoplasty or lobectomy, the results in such combined operations will also be considered.

MATERIAL FOR STUDY AND CLASSIFICATION

Because there are significant clinical and pathological differences between tuberculous and nontuberculous pleural disease, the cases that follow will be divided into these two categories.

TABLE 1

Physical Characteristics and Clinical Diagnosis in 9 Cases Treated with Decortication

CASE	SEX	AGE	HEIGHT	WEIGHT	BODY SURFACE	DIAGNOSIS
			cm.	kg.	m^2	
1. L. C.	M	38	173	58.5	1.70	Spontaneous hemopneumothorax, right, early
2. J. J.	M	24	185.5	76	1.99	Spontaneous hemothorax, right early
3. H. N.	M	30	179	65	1.82	Traumatic hemothorax, right, early
4. H. C.	M	51	165	58	1.64	Hemothorax, left, old Pulmonary emphysema
5. C. C.	F	30	160	50.5	1.51	Pneumococcus type 7 empyema, left Tuberculous empyema, left
6. H. P.	M	50	167	60	1.65	Tuberculous empyema, left
7. F. H.	M	20	178	61.5	1.78	Pulmonary tuberculosis, left Spontaneous pneumothorax, left, with tuberculous empyema
8. F. M.	M	32	170	63	1.73	Pulmonary tuberculosis, right Right ? hemothorax or ? tuberculous empyema
9. L. M.	M	43	175	57	1.68	Pulmonary tuberculosis, left Left tuberculous empyema

The nontuberculous group consists of 4 patients: 2 with spontaneous hemothoraces, one with a traumatic hemothorax, and one with an old hemothorax which was probably secondary to trauma (table 1).

Five patients with tuberculous pleural disease were studied (table 1). At the time of operation, none had active tuberculosis. Three had decortication alone; one had decortication followed by thoracoplasty; and one had decortication with lobectomy, and later a thoracoplasty.

Methods

The methods used in this study have been described previously by Baldwin, Cournand, and Richards (3). In addition, the oxygen-tension difference between alveolar air and arterial blood was determined by the method of Riley, Lilienthal, and others (4, 5, 6).

Because mixed venous blood was not obtained by right-heart catheterization in these cases, the analysis of the pulmonary diffusion and of ventilation-perfusion relationships by the method described by Riley and others (6, 7, 8) was not carried out. The physiological dead space was calculated according to a modified BoR_2 formula used in this laboratory.

RESULTS

Hemothorax

In the first 3 cases to be reported, decortication was performed within two months of the onset of hemothorax. Physiologic measurements after decortication were normal in the first 2 cases, and nearly normal in the third. In the fourth case, decortication was done several years after the onset of the pleural disease. The final state of pulmonary function attained by this patient was not as satisfactory as in the preceding cases.

Case 1. A 38-year-old white male had been well until May 8, 1948, when he had sudden pain in the right chest while sitting quietly. He became dyspneic and weak, and was admitted to a hospital. A right hydropneumothorax was demonstrated roentgenographically (figure 1a), and 4,000 cc. of thick dark blood were obtained in three thoracenteses. Thereafter it became impossible to obtain fluid by thoracentesis. On June 20, 1948, the lung was still incompletely expanded (figure 1b), with thickened pleura over the right lower lobe. Decortication was carried out on June 28, 1948, seven weeks after the onset of the illness. A large amount of "peel"[4] and blood clots were removed from the costophrenic sinus. The right lung expanded completely (figure 1c), and there were no postoperative complications thereafter.

Studies of pulmonary function: The various measurements of lung function six months after operation were normal (table 2).

Case 2. A 24-year-old white college student, previously in good health, experienced the gradual onset of dull pain between the shoulder blades while walking on June 11, 1948. The pain increased and localized in the left upper chest and left upper quadrant. Because of these complaints, he entered the hospital. Two transfusions were given, and a thoracentesis yielded pure blood. In spite of three subsequent thoracenteses, a density persisted over the left lower lung field (figure 2a).

A decortication was performed on July 26, 1948, approximately six weeks after the first symptoms appeared. The surface of the collapsed left lung was covered by an organized membrane which was particularly thick in the costophrenic sinus and over the surface of the diaphragm. Complete decortication was carried out. Sections of the removed material showed chronic pleuritis with evidence of old hemorrhage. The lung expanded well (figure 2b), and there were no postoperative complications.

Studies of pulmonary function: As in the previous case, all measurements of pulmonary function done five months after operation were normal (table 2).

Case 3. A 30-year-old Negro male fell down a flight of stairs in May 1948 and sustained a fracture of the seventh, eighth, ninth and tenth ribs on the right. Within several days fluid accumulated in the right pleural space. Because the fluid persisted after a month of observation, he was referred to Bellevue Hospital on June 16, 1948. A hemothorax and rib fractures were found on the right side and 1,100 cc. of bloody fluid were removed (figure 3a). Following thoracentesis, loculation of the fluid was noted.

[4] This term is used to describe all of the organized pathological structures removed during pleural decortication.

Decortication was performed on June 29, 1948, approximately seven weeks after the injury. The lung was compressed by thick, fibrinous material which was removed. Histologic examination showed that this material was an organized hematoma. The postoperative course was uncomplicated.

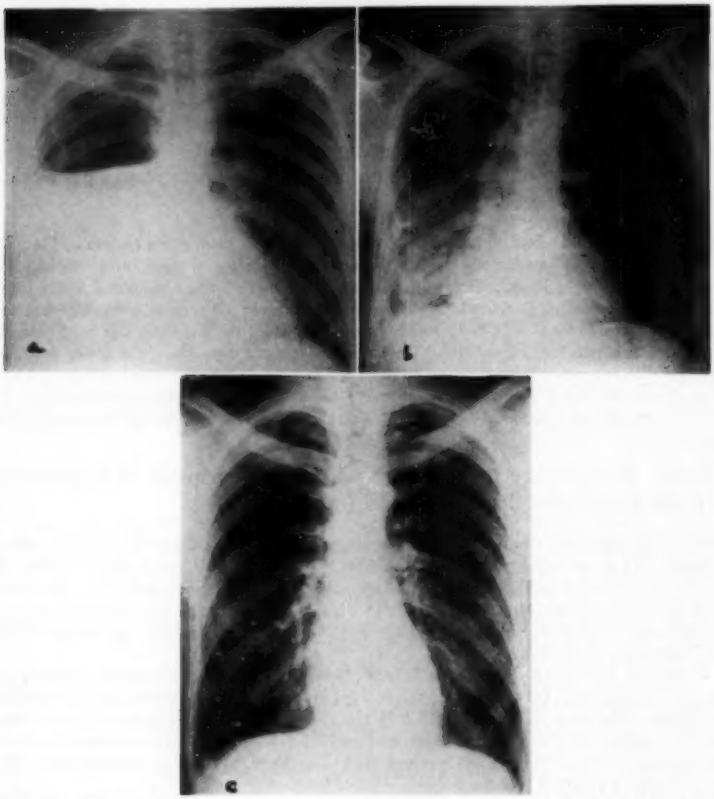

FIG. 1a. Chest roentgenogram of Case 1 before treatment. b. Case 1 after three thoracenteses. c. Case 1 six months after decortication. (For description see text.)

Studies of pulmonary function: Pulmonary function studies were performed two weeks, and again six months, after operation (table 3). The only abnormalities on the first study consisted of: a slight increase in the residual air; a slight decrease in the total capacity; and a residual air/total capacity ratio (RA/TC $\times$ 100) of 33 per cent.

Six months after operation the chest roentgenogram was nearly normal (figure 3b), and the abnormalities of pulmonary function were no longer present.

TABLE 2

Physiological Measurements in 2 Cases of Hemothorax Treated Early with Decortication

	CASE 1 6 MONTHS POSTOPERATIVE		CASE 2 5 MONTHS POSTOPERATIVE	
	Observed	Predicted	Observed	Predicted
I. Lung volumes in cc.				
Vital capacity	4,760	4,540	4,660	5,380
Residual air	1,909	1,120	1,241	1,330
Total capacity	6,668	5,660	6,001	6,710
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	29	20	21	20
II. A. Maximum breathing capacity in L/min	170	119	152	147
B. Ventilation in L/min/m² B.S.				
Basal	4.1	3.1	3.9	3.6
1 minute standard exercise	9.4	10.0	11.7	11.0
First minute recovery	12.4	13.4	11.0	12.5
C. Breathing reserve in liters				
1 minute standard exercise	154	102	129	125
First minute recovery	136	96	114	122
III. A. Index of intrapulmonary mixing				
Alveolar N_2, per cent	0.9	<2.5	1.2	<2.5
B. Arterial blood oxyhemoglobin saturation, per cent				
Basal	97	96	97	96
First minute recovery	95	96	95	96
IV. Oxygen removal in cc/L/ventilation				
Basal	41.3	46.1	45.1	47.1
1 minute standard exercise	62.1	55.7	64.1	56.2
V. Alveolo-arterial gradient, mm. of mercury				
Breathing room air	7	<12	14	<12
Breathing low oxygen	2*	<12	5*	<12
Physiological dead space in per cent of tidal air	22	30	24	30
VI. Bronchospirometry, right lung				
Per cent of total vital capacity	52	55	59	55
Per cent of total ventilation	51	55	55	55
Per cent of total oxygen intake	50	55	58	55

* Inspired air contained 12 per cent oxygen.

Bronchospirometry, performed for the first time, showed a slight decrease in the oxygen intake on the operated side.

Comment: In the preceding 3 cases, decortication was performed in patients with uncomplicated hemothorax after aspiration had failed to result in expan-

sion of the lung. The operation was performed within two months of the probable onset of the hemothorax. Within six months after operation, 2 patients had normal lung function. In the third patient the evidence of distention of the lung (RA/TC ration of 33 per cent) two weeks after operation was probably due

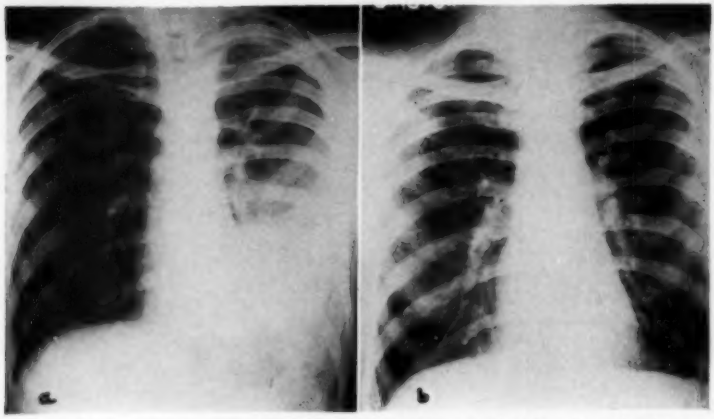

FIG. 2a. Case 2 before decortication. b. Case 2 six months after decortication.

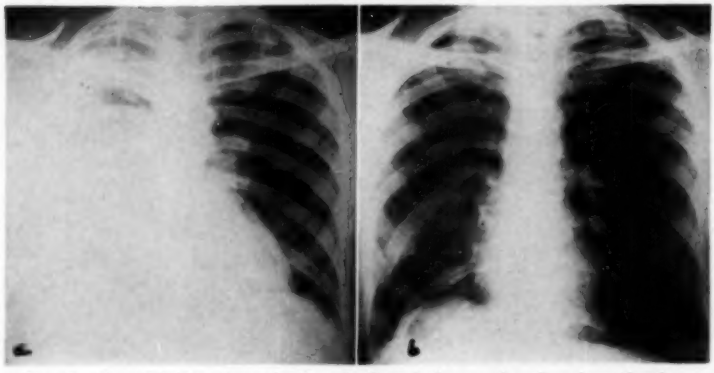

FIG. 3a. Case 3 before decortication. b. Case 3 six months after decortication.

to some limitation in diaphragmatic and chest wall motion during the early postoperative period. This defect was no longer present five months later. The moderate decrease in the oxygen intake on the operated side in one case suggested that the return of normal circulation to that side was not complete.

Case 4. A 51-year-old male entered the hospital April 22, 1947 complaining of right lower chest pain and productive cough of two weeks' duration. Fifteen years before, he had had

TABLE 3

Physiological Measurements in 2 Cases of Hemothorax; One Treated Early, and One Treated Late with Decortication

	CASE 3			CASE 4		
	1 month post-operative	6 months post-operative	Predicted	4 months pre-operative	1 month post-operative	Predicted
	Observed	Observed		Observed	Observed	
I. Lung volumes in cc.						
Vital capacity	3,252	4,165	5,000	1,634	1,400	3,750
Residual air	1,641	1,389	1,240	1,951	882	1,210
Total capacity	4,916	5,785	6,240	3,667	2,326	4,960
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	33	24	20	53	38	24
II. A. Maximum breathing capacity in L/min	150	149	129	86	95	97
B. Ventilation in L/min/m² B.S.						
Basal	4.7	4.8	3.6	5.5	5.0	3.9
1 minute standard exercise	13.0	11.1	11.0	19.3	15.1	11.2
First minute recovery	16.8	9.4	12.5	21.1	21.8	14.5
C. Breathing reserve in liters						
1 minute standard exercise	126	128	109	54	71	79
First minute recovery	117	123	106	27	52	73
III. A. Index of intrapulmonary mixing						
Alveolar N_2, per cent	1.1	2.2	<2.5	2.8	1.8	<2.5
B. Arterial blood oxyhemoglobin saturation, per cent						
Basal	98	98	96	91	89	96
First minute recovery	98	95	96	84	82	96
IV. Oxygen removal in cc/L/ventilation						
Basal	41.3	34.3	47.1	33.7	31.1	38.5
1 minute standard exercise	53.4		56.2	47.0	37.0	53.2
V. Alveolo-arterial gradient, mm. of mercury						
Breathing room air		16	<12	21	37	<12
Breathing low oxygen		15*	<12	23†	17†	<12
Physiological dead space in per cent of tidal air		33	30	50	49	30
VI. Bronchospirometry, right lung						
Per cent total vital capacity		48	55	87	73	55
Per cent total ventilation		54	55	83	58	55
Per cent oxygen intake		33	55	93	70	55

* Inspired air contained 12 per cent oxygen.

† Inspired air contained 14 per cent oxygen.

pleurisy. Ten years later, he had been admitted to another hospital with a traumatic fracture of a dorsal vertebra. While in a body cast, cough and pain in the left chest developed. Following removal of the cast, there was mild exertional dyspnea and some increase in cough. Both of these complaints persisted during the next five years until hospital admission was precipitated by a sudden increase in cough and right pleuritic chest pain.

On admission, the temperature was 101° F., rales were heard over the right lower chest, and physical and roentgenographic examinations revealed evidence of pleural effusion and fibrosis at the left base. A quick symptomatic response followed penicillin, and the patient was discharged without further treatment.

Readmission to the hospital on November 5, 1947 resulted from a recurrence of acute respiratory symptoms and an increase in dyspnea. The physical examination and chest roentgenogram (figure 4a) had not changed, and again a quick response to penicillin occurred. Thoracentesis on several occasions yielded small amounts of serous fluid with a specific gravity of 1.018 with small numbers of leukocytes, predominantly lymphocytes. Repeated cultures of the pleural fluid were negative for tubercle bacilli. Bronchograms showed no evidence of bronchiectasis. Because of the presence of chronic pleural disease

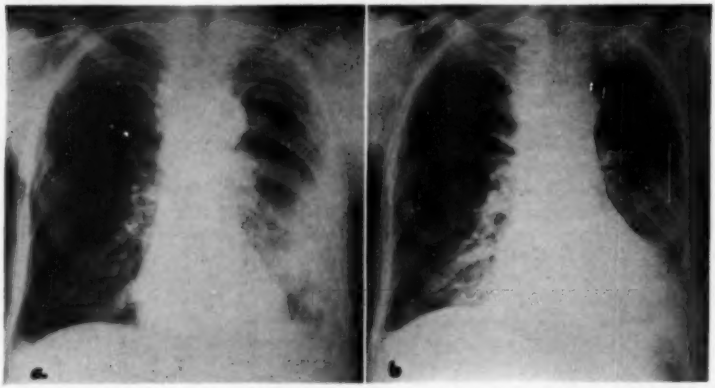

FIG. 4a. Case 4 before decortication. b. Case 4 three weeks after decortication.

and a collapsed lung, it was decided to undertake decortication. The cause of the pleural disease was believed to be chronic, organizing hemothorax, secondary to the injury five years before.

Studies of pulmonary function: Pulmonary function studies done on February 25, 1948 (table 3) showed: (*1*) a reduction in the vital capacity and total capacity; (*2*) an increase in the residual air with an elevated RA/TC ratio; (*3*) a marked reduction in the arterial blood-oxygen saturation at rest, and still further reduction after standard exercise; (*4*) an abnormal increase in the alveolar arterial oxygen-tension gradient while breathing both room air and a low oxygen mixture; (*5*) an elevation of the physiological dead space to 50 per cent of the tidal air; and (*6*) a reduction of the ventilation and oxygen intake of the left lung to 17 and 7 per cent of the total ventilation and oxygen intake, respectively.

Decortication of the lung was performed on July 6, 1948. A hyaline membrane 2 to 4 cm. in thickness was removed by sharp dissection from the entire lung

and showed chronic inflammation with fibrosis, hyalinization, and calcification of the pleura. Following operation, the patient was cyanotic and oxygen therapy was required for several days, but ultimately the lung expanded well (figure 4b). Some pain persisted in the left chest for several weeks.

Function studies were repeated on July 26, 1948 (table 3) and showed the following changes: (*1*) a further reduction in the vital capacity and total capacity and a reduction in the residual air; (*2*) a reduction of the RA/TC ratio to 38 per cent; (*3*) a decrease to normal levels in the nitrogen concentration in alveolar air after seven minutes of pure oxygen breathing; (*4*) a persistence of the arterial blood-oxygen unsaturation at rest and after the standard exercise test; (*5*) a continued elevation of the alveolar arterial oxygen-tension gradient while breathing room air and a low oxygen mixture; (*6*) a marked increase in the per cent of total ventilation and oxygen intake performed by the left lung.

Comment: The studies on this patient show that improvement of function occurred after decortication of a lung which had been incarcerated for a long period of time. The improvement is established by the percentage increase of the total ventilation and oxygen intake performed by the left lung. There was, however, still evidence of blood flow through poorly ventilated areas. Lung volumes and MBC were determined too soon after operation for the findings to be conclusive, but there was evidence from the residual air volume and alveolar nitrogen per cent concentration after breathing pure oxygen that distended areas in the lung had been released.

Tuberculous Pleural Disease

Five cases of tuberculous pleural involvement were studied. Two of the patients were without significant pulmonary tuberculosis, one was treated early, and the other late, in the course of the illness. One patient with underlying pulmonary tuberculosis was treated by decortication alone, and 2 other patients had decortication combined with thoracoplasty or with lobectomy and thoracoplasty.

Case 5. A 30-year-old Porto Rican female, pregnant and near term, came to the hospital on June 21, 1948 complaining of pain in the chest, with dyspnea for twelve hours. A slightly productive cough and mild night-sweats had been present for one month. A chest roentgenogram obtained in December 1947 had been normal.

A pleural effusion was found on the left which yielded type 7 pneumococcus on culture. A diagnosis of pneumococcal empyema secondary to a resolved pneumococcal pneumonia was made (figure 5a). The patient was given penicillin by the intramuscular and intrapleural routes. Shortly after admission, she was delivered of a normal child.

Despite penicillin therapy, fever persisted and the presence of tuberculosis was suspected. Both sputum and pleural drainage were negative for tubercle bacilli on culture. On July 31, 1948, steptomycin, 1 gm. daily, was started and was continued for six weeks. Because of the failure of the empyema to clear completely on a regimen of aspiration and antimicrobial therapy, decortication of the left lung was performed on August 2, 1948, approximately six weeks after the onset of the illness. The empyema cavity was evacuated. Histologic examination of the tissue removed at decortication showed caseation necrosis with tubercle formation. Culture of the empyema exudate was positive for tubercle bacilli. The postoperative course was uneventful. The patient became afebrile on the thirteenth

postoperative day, gained weight, and was free of respiratory symptoms at the end of her hospitalization. A roentgenogram of the chest showed nearly complete expansion of the lung (figure 5b).

Studies of respiratory function: Respiratory function studies done on September 10, 1948, approximately six weeks after the operation (table 4), showed these abnormalities: a slight reduction of the vital capacity and total capacity; a decrease in the per cent of oxygen intake in the left lung to 31 per cent of the total oxygen intake, with persistence of the normal fraction of ventilation on that side.

Case 6: A 50-year-old male was well until September 1947, when he noted the gradual onset of dyspnea, chills, and fever. Pain developed in the left side of the chest. Pneumonia was diagnosed and four thoracenteses were done on the left. In December an open thoracotomy with drainage was done. The wound continued to drain. The patient was able to work, however, and felt well from June 1948 until he was admitted to the hospital on July 19, 1949 because of continued drainage from the chest.

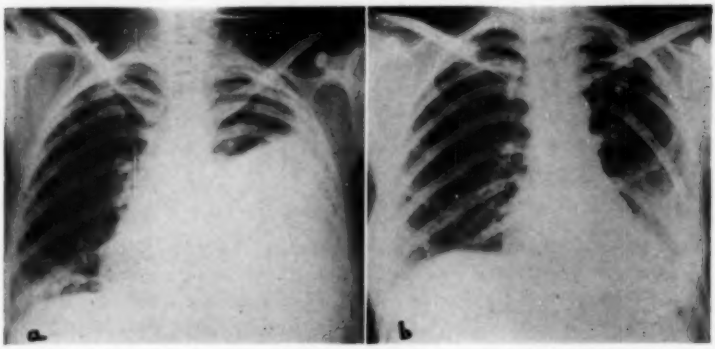

FIG. 5a. Case 5 before decortication. b. Case 5 one month after decortication.

On examination, a draining wound along the course of the left tenth rib was present. There was a thick, non-foul, yellow discharge. The chest roentgenogram (figure 6a) revealed a left pneumothorax with thickened pleura. Culture of the discharging sinus was positive for tubercle bacilli.

Streptomycin, 1 gm. daily, was started on July 25, 1949 and continued for forty-two days. On September 14, 1949, two years after the onset of the illness, decortication was done. The left lung was found to occupy approximately one-half of the left chest. It was covered by a thick membrane which was difficult to peel, and decortication was done by sharp dissection. Microscopic examination of the material removed at operation revealed tuberculosis of the pleura with fibrosis of the peripheral lung tissues and sinus tract formation. The entire lung was mobilized, but many constricting bands remained over the lower lobes, preventing full expansion of the lung. In addition, numerous alveolar leaks were present due to the difficult dissection. During the operation, the advisability of performing a pneumonectomy was considered but, since full expansion was believed possible, it was not done. Following operation, the lung did not completely expand despite suction (figure 6b).

TABLE 4

Physiological Measurements in 3 Cases of Tuberculous Pleural Disease, Treated by Decortication

	CASE 5 4 MONTHS POST-OPERATIVE		CASE 6 3 MONTHS POST-OPERATIVE		CASE 7 13 MONTHS POST-OPERATIVE	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
I. Lung volumes in cc.						
Vital capacity	2,271	3,050	2,610	3,860	2,975	4,940
Residual air	1,064	1,070	1,135	1,240	977	1,220
Total capacity	3,444	4,120	3,795	5,100	3,768	6,160
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	31	26	30	23	26	20
II. A. Maximum breathing capacity in L/min.	92	86	61	100	116	135
B. Ventilation in L/min/m² B.S.						
Basal	5.4	3.2	5.4	3.9	4.2	3.6
1 minute standard exercise	15.5	9.0	16.9	11.2	10.3	11.0
First minute recovery	16.9	10.9	13.2	14.5	14.3	12.5
C. Breathing reserves in liters						
1 minute standard exercise	68	72	42	82	98	115
First minute recovery	42	70	39	76	99	113
III. A. Index of intrapulmonary mixing						
Alveolar N_2	0.6	<2.5	0.9	<2.5	1.0	<2.5
B. Arterial blood oxyhemoglobin saturation, per cent						
Basal	96	96	96	96	96	96
First minute recovery	98	96	94	96	95	96
IV. Oxygen removal in cc/L/ventilation						
Basal	32.8	45.1	31.9	38.5	38.5	47.1
1 minute standard exercise	38.6	60.2	34.6	53.2	48.3	56.2
V. Alveolo-arterial gradient, mm. of mercury						
Breathing room air	16	<12			13	<12
Breathing low oxygen	3*	<12			2*	<12
Physiological dead space in per cent of tidal air	30	30			25	30
VI. Bronchospirometry, right lung						
Per cent total vital capacity	75	55	80	55	66	55
Per cent total ventilation	56	55	65	55	74	55
Per cent total oxygen intake	69	55	86	55	73	55

* Inspired air contained 12 per cent oxygen.

Studies of pulmonary function: Pulmonary function studies (table 4) one and one-half months after operation showed the following defects: (*1*) a reduction of

the vital capacity and the total capacity; (*2*) a reduction in the MBC to 61 per cent of the predicted normal; (*3*) dyspnea for more than two minutes after the standard exercise test; and (*4*) reduction of the ventilation and oxygen intake of the left lung to 35 and 14 per cent of the total ventilation and oxygen intake, respectively.

The decortication was unsuccessful in completely expanding the lung. On January 11, 1950, a muscleplasty with removal of anterior segments of the second and third ribs was done. The lung remained unexpanded. A period of bed rest was recommended before any decision as to further surgery was made. The patient left the hospital against advice on February 5, 1950.

Comment: In the 2 preceding cases the patients had tuberculous pleural disease with little evidence of parenchymal disease, and they were treated with

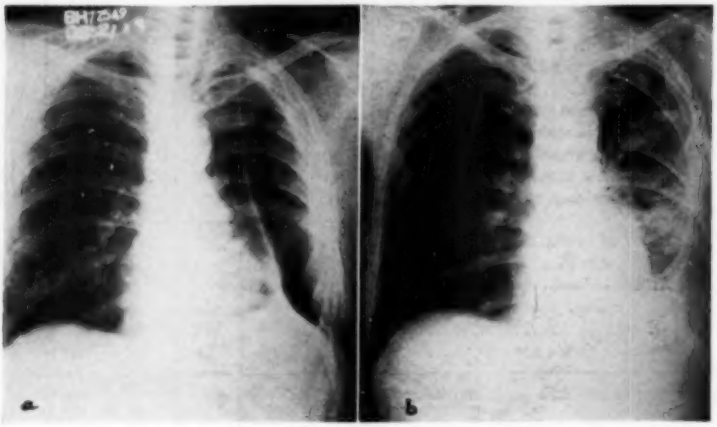

FIG. 6a. Case 6 before decortication. b. Case 6 two and one-half months after decortication.

decortication. The final results in the 2 cases were quite different. In the first case, a reduction in the vital capacity and the oxygen intake on the affected side was the only residual physiologic defect. This was the best functional result obtained in any of the tuberculous cases, but was not as good as the results in early hemothorax cases after decortication. In this tuberculous patient (Case 5), decortication was performed early after the onset of the empyema, thus limiting the extent of pleurogenic fibrosis.

In contrast, the second patient (Case 6) had a poor clinical and physiological result from decortication, which was not performed until two years after the onset of the empyema. The course of this patient's pleural disease had been further complicated by an open thoracotomy with a draining sinus. The striking physiologic findings were a reduction in the efficiency of the chest bellows, a marked reduction of lung volume on the left, and a much greater reduction of blood perfusion on that side.

Case 7. A 20-year-old Negro entered the hospital July 23, 1947 complaining of left anterior chest pain of two weeks' duration. Since May 1947 he had noted a moderately productive cough and had had two recent episodes of hemoptysis. A cavity was found in the lower lobe of the left lung, and the sputum contained acid-fast bacilli.

On August 17, a spontaneous pneumothorax developed on the left (figure 7a). Fluid accumulated rapidly, and tubercle bacilli were cultured from it. Streptomycin, 1 gm. daily, was started on August 19 and continued until December 19, 1947. Dyspnea persisted and the intrapleural pressures increased following the removal of air. For this reason a closed thoracotomy with a water seal was instituted, and the lung re-expanded. Fluid continued to accumulate, and the expansion of the lung could not be maintained. During this time, the cavity in the left lower lobe could not be identified. Sputum and gastric contents were negative for tubercle bacilli on culture. A decortication was performed on November 26, 1947, fourteen weeks after the occurrence of the spontaneous pneumothorax. No difficulty was encountered at operation, and re-expansion was excellent (figure 7b).

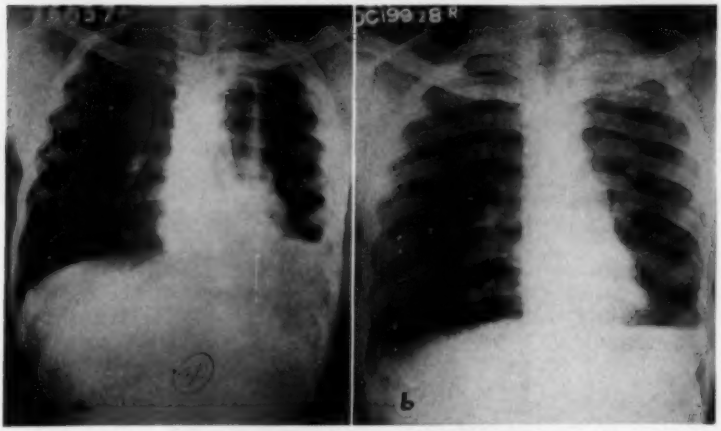

FIG. 7a. Case 7 after spontaneous pneumothorax. b. Case 7 one year after decortication.

Studies of respiratory function: Respiratory studies (table 4) one year after decortication revealed the following defects: (*1*) a moderate reduction in the vital capacity, residual air, and total capacity; (*2*) a slight reduction of the MBC; and (*3*) an equal reduction of the ventilation and oxygen intake of the left lung to 27 per cent of the total ventilation and the total oxygen intake.

Comment: Although full function was not restored in this patient after decortication, there was no serious disturbance in ventilation-perfusion relationships and the disease was adequately controlled. The persistent physiological abnormalities are of a degree commonly seen with parenchymal tuberculosis of comparable extent.

Case 8. A 32-year-old Porto Rican male entered the hospital in July 1946 complaining of cough and weight loss for six months. An infiltration at the right apex of the lung between the second and fourth posterior ribs (figure 8a) was found. Cavitation developed in this area, and the sputum contained acid-fast bacilli. A right pneumothorax was started in November 1946. Pneumonolysis in December was followed by nearly complete collapse of

the lung and rapid accumulation of bloody pleural fluid. Repeated thoracenteses in the next year were unsuccessful in re-expanding the lung (figure 8b). Sputum and pleural fluid remained negative for tubercle bacilli. Decortication was performed on February 17, 1948. Streptomycin, 1 gm. daily, was started on this day and continued for forty-two days.

At operation, the pleural cavity was found to be lined with a thick avascular membrane, 1 cm. thick in some places. Approximately 150 cc. of serosanguineous fluid were present.

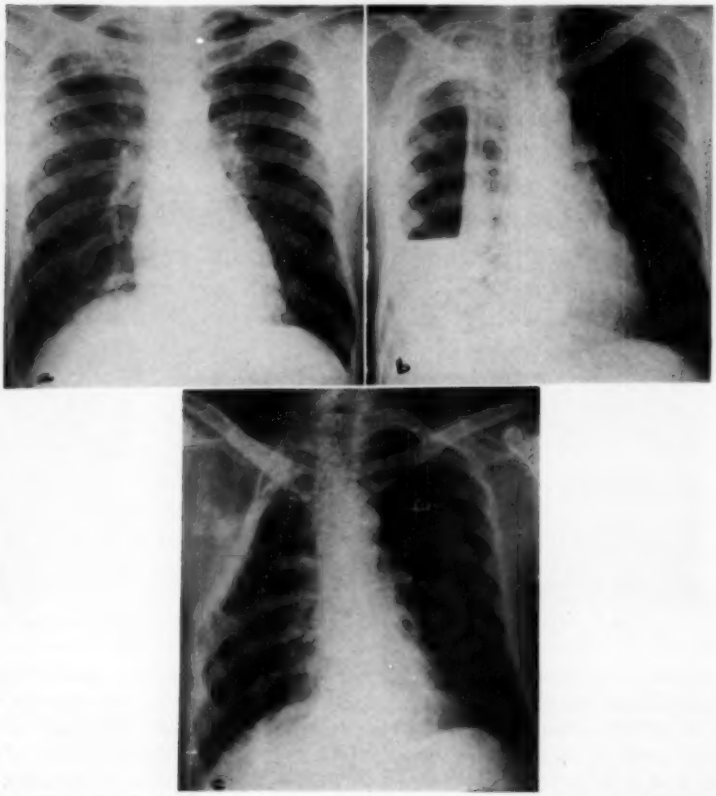

FIG. 8a. Case 8 before therapeutic pneumothorax. b. Case 8 after therapeutic pneumothorax. c. Case 8 seven months after decortication and thoracoplasty.

A good cleavage plane was established between the lung and the visceral pleura, and decortication was complete except at the extreme apex. The material removed at operation revealed chronic inflammatory reaction with fibrosis and hyalinization, but no evidence of tuberculosis. Following operation the lung expanded well, except at the extreme apex where some fluid accumulated. Because of the fluid and the presence of an old tuberculous focus at the apex, a five-rib thoracoplasty was done in two stages on February 26 and March 16.

By April 1948, the patient's cough had disappeared; he had gained nineteen pounds in weight, and a roentgenogram of his chest (figure 8c) showed no parenchymal disease.

Studies of pulmonary function: Pulmonary function studies were done in June 1948 (table 5) and the following abnormalities only were found: (*1*) a moderate reduction in the vital capacity and total capacity; (*2*) a slight elevation of the RA/TC ratio to 34 per cent; (*3*) a limitation in the MBC to 65 per cent of the predicted value; (*4*) the presence of dyspnea for more than one minute after the standard exercise test.

Function studies were repeated three months later (table 5) with the following significant findings: (*1*) an increase in the MBC to 78 per cent of the predicted normal value; (*2*) the absence of dyspnea after the standard exercise test; (*3*) bronchospirometry, done for the first time, showed a reduction in the ventilation and oxygen intake of the right lung to 44 and 29 per cent of total ventilation and total oxygen intake, respectively.

Comment: This patient had parenchymal tuberculosis, but there was no evidence of tuberculosis found on histologic examination of the decorticated material. Except for the underlying parenchymal tuberculosis, the therapeutic problem resembled that seen in uncomplicated hemothorax. The limited parenchymal involvement probably accounted for the minor functional abnormalities. In particular, the reduced oxygen intake on the right side was presumably due to a decrease in the blood flow to that lung.

Case 9. A 43-year-old Porto Rican male developed tuberculosis in the left lung two and one-half years before admission to the hospital. A pneumothorax had been started approximately a month after the diagnosis had been made but, because of accumulation of fluid, it was discontinued. The patient felt well and had no further medical supervision until a routine roentgenogram of the chest (figure 9a) resulted in admission to the hospital in April 1949.

A diagnosis of left tuberculous empyema secondary to therapeutic pneumothorax was made. Tubercle bacilli could be cultured from the empyema fluid, but not from the sputum.

Studies of lung function: Lung function studies were done early in October 1949 (table 5) before operation and showed the following abnormalities: (*1*) a reduction in the vital capacity and total capacity; (*2*) a decrease of the MBC to 57 per cent of the predicted normal value; (*3*) dyspnea for one and one-half minutes after the standard exercise test; and (*4*) a reduction of the ventilation and oxygen intake on the left side to 19 and 10 per cent of the total ventilation and total oxygen intake, respectively.

Streptomycin was started early in December, and on December 22, 1949 a decortication of the left lung with resection of the left upper lobe and the dorsal segment of the left lower lobe was performed. Microscopic examination of the material removed at operation showed some calcification of the pleura, with thickening of the parietal pleura. The lung parenchyma contained several firm nodular as well as fibrocaseous tuberculous areas.

Because of a persistent space at the left apex, a thoracoplasty was done with removal of the second to fifth ribs on January 13, 1950. The patient did well

TABLE 5

Physiological Measurements in 2 Cases of Tuberculous Pleural Disease Treated by Decortication, Combined with Thoracoplasty, or Thoracoplasty and Lobectomy

	CASE 8			CASE 9			
	4 months post-operative	6 months post-operative	Predicted	2 months pre-operative	1 month post-operative	2 months post-operative	Predicted
	Observed	Observed		Observed	Observed	Observed	
I. Lung volumes in cc.							
Vital capacity	2,546	2,425	4,475	2,623	2,090	2,193	4,270
Residual air	1,348	1,132	1,105	1,324	1,357	1,074	1,380
Total capacity	3,973	3,690	5,580	4,136	3,533	3,419	5,650
$\frac{\text{Residual air}}{\text{Total capacity}} \times 100$	34	31	20	32	38	31	24
II. A. Maximum breathing capacity in L/min	78	94	121	65	63	57	117
B. Ventilation in L/min/m² B.S.							
Basal	5.0	4.0	3.6	3.9	3.5		3.1
1 minute standard exercise	12.2	11.9	11.0	10.9	15.2		10.0
First minute recovery	15.5	12.7	12.5	18.1	14.2		13.4
C. Breathing reserve in liters							
1 minute standard exercise	57	73	102	47	38		100
First minute recovery	40	64	99	35	28		94
III. A. Index of intrapulmonary mixing							
Alveolar N_2	1.6	1.3	<2.5	1.6	1.4	1.2	<2.5
B. Arterial blood oxyhemoglobin saturation, per cent							
Basal	98	94	96	97	95		96
First minute recovery	98	98	96	95	94		96
IV. Oxygen removal in cc/L/ventilation							
Basal	28.8	37.0	47.1	36.6	35.2		46.1
1 minute standard exercise	48.7	44.6	56.2	46.3	32.7		55.7
V. Alveolo-arterial gradient, mm. of mercury							
Breathing room air	15	15	<12		5		<12
Breathing low oxygen	7*	9*	<12		2†		<12
Physiological dead space in per cent of tidal air	29	28	30		33		30
VI. Bronchospirometry, right lung							
Per cent of total capacity		42	55	89	93		55
Per cent of total ventilation		44	55	81	83		55
Per cent of total oxygen intake		29	55	90	85		55

* Inspired air contained 12 per cent oxygen.

† Inspired air contained 16 per cent oxygen.

clinically thereafter and a roentgenogram (figure 9b) showed expansion of the remaining lung on the left.

Respiratory studies were done early in February 1950 (table 5) after both decortication and thoracoplasty and showed: (*1*) a slight reduction in the vital capacity, residual air, and total capacity from the preoperative studies; (*2*) a slightly elevated physiological dead space; (*3*) no significant change from the preoperative studies in the oxygen intake or the ventilation on the left side.

Comment: Decortication was combined with lobectomy and thoracoplasty in this 43-year-old man with tuberculous empyema secondary to therapeutic pneumothorax of two and one-half years' duration. The final result, which shows no change in the pulmonary function from the preoperative state, cannot be attributed solely to decortication. The persistence of small lung volume and a

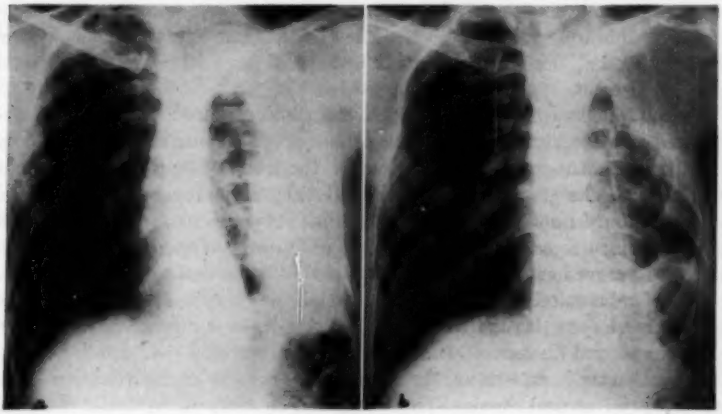

FIG. 9a. Case 9 before decortication. b. Case 9 two months after decortication, lobectomy, and thoracoplasty.

small oxygen intake in the remaining left lung could be due to the residual effect of pleural disease or to earlier parenchymal disease in the left lower lobe.

DISCUSSION

The therapeutic aims in pleural disease may be classified as follows:

1) release and expansion of the collapsed lung from its fibrous, fibrinous, or fluid encasement;

2) re-establishment of intrathoracic spatial relationships so that displacement of the mediastinum and collapse or overdistention of the contralateral lung is prevented;

3) control of infection, if present, by evacuation and obliteration of the pleural space; and

4) proper treatment of any underlying pulmonary parenchymal disease which may exist.

Pleural decortication, either alone or in conjunction with lobectomy or thoracoplasty in selected cases, is the only surgical procedure which allows treatment with regard to all of these considerations.

At least three factors are important in estimating the likelihood of success in decortication: the nature of the pleural disease, for example, whether infected or noninfected, whether suppurative or nonsuppurative; the presence or absence of underlying parenchymal disease; and the duration of the pleural process.

The first factor is different in hemothorax and tuberculous pleural disease. Hemothorax, at least in the early stages, is primarily a disorder of the surface of the pleura, while tuberculous pleural disease may involve all layers of the pleura. The less extensive the pleural involvement, the more likely is a successful outcome following decortication. In two of the writers' cases of hemothorax and in one of Wright's (2) two cases, the function was restored to nearly normal limits. In the writers' cases, in which tuberculous pleural disease was present without parenchymal tuberculosis, return of function was not so great as in the cases of hemothorax but was greater than the resulting function when parenchymal disease was present.

The second factor (underlying parenchymal disease) is also different in hemothorax and in tuberculous pleural disease. The parenchyma of the lung is seldom involved in hemothorax, while it is usually the site of origin for tuberculous pleural disease. The greater the parenchymal disease, the less likely is return of normal function. In none of the 5 patients with tuberculous pleural disease and underlying lung tuberculosis reported by Gordon and Welles (1) was there a significant improvement in pulmonary function after decortication. In the writers' cases of tuberculosis of both the pleura and the lung, the resulting function after successful decortication has been less than in hemothorax or in isolated tuberculous pleural disease.

The third factor in estimating the likelihood of success in decortication is the duration of the pleural disease. There is evidence from pathological material that, with the passage of time, pleural fibrosis extends into the lung along the lobular septa and limits further the expansibility of the lungs. This is true both in hemothorax and in tuberculous pleural disease.

Case 4 is the first reported case of hemothorax of long duration which was studied before and after decortication. While this case shows that some pulmonary function may be restored by decortication after many years of incarceration by a hemothorax, it also shows how much the passage of time interferes with complete restoration of normal function.

The effect of early treatment of tuberculous pleural disease is shown in Case 5, in which the final physiological status was the best which has been observed in any case of tuberculous pleural disease reported to date.

From a consideration of these factors, as illustrated in the cases reported here, certain generalizations about therapy in pleural disease may be made:

In hemothorax, decortication has proved so successful that it should be resorted to early, before fibrosis has extended beyond the pleura. If a hemothorax has been neglected and is seen for the first time after a considerable lapse of time, some function may still be restored by decortication.

The best physiological results obtained by decortication in tuberculosis will probably be observed in those cases which are treated as early as possible, provided that the pleural disease is either not complicated by parenchymal disease or is so located that it may be simultaneously treated by some other means, such as thoracoplasty or lobectomy. Certain cases (Case 9 in the present series and several cases reported by Gordon and Welles) will be seen in which there has been widespread tuberculosis of the lung, and in which the disease is of considerable age. In such cases, the pleural disease may be controlled by decortication combined with other procedures, but the residual function may be so small after these procedures as to raise the question of whether total extrapleural pneumonectomy would not have been a better procedure.

The material in the present study on decortication also provides an opportunity for analysis of some of the physiological defects which may characterize untreated or incompletely treated pleural disease. The principal defects observed in such cases have been in ventilatory function. The alterations have consisted of: (*1*) reduction in the vital capacity and total capacity; (*2*) occasional slight increases in the residual air to total capacity (RA/TC × 100); (*3*) slight decrease in the maximum breathing capacity; (*4*) slight decreases in the efficiency of ventilation as manifested by a decrease in the amount of oxygen removed from each liter of inspired air.

The only evidence found in this study of a significant disturbance of the ventilation-perfusion relationship which could be ascribed to the pleural disease has come from bronchospirometry. Wright has reported one case, however, in which arterial blood-oxygen unsaturation seems to have been due to the pleural process. In the present study, the patient (Case 4) with arterial blood-oxygen unsaturation and elevated alveolar-arterial oxygen-tension gradients clearly had underlying associated disease, which could have accounted for this defect. On bronchospirometry, it was found that among the cases in which there was not complete return of function, greater improvement was often noted in the ventilation on the affected side than in the oxygen intake. This defect in ventilation-perfusion relationships may be seen in Cases 3, 4, 5, 6, and 8. The defect was also present in the two cases reported by Wright in which function remained abnormal after decortication, and in all but one of Gordon and Welles' cases in which post-decortication bronchospirometry was performed.

SUMMARY

Pulmonary function studies on 9 patients with pleural disease treated by decortication are reported. Three patients operated on soon after the onset of hemothorax regained normal function. One patient with a hemothorax of long standing showed improved function after decortication, but not a return to normal.

Five patients with various types of tuberculous pleural disease were studied. Those with no demonstrable parenchymal disease and with pleural disease of the shortest duration had the best functional results. In one case thoracoplasty was combined with decortication, resulting in control of the pleural and parenchymal disease and in moderately good function. One patient who had a decorti-

cation combined with lobectomy had a good clinical outcome, but a relatively poor functional result.

SUMARIO

La Función Pulmonar consecutivamente a la Decorticación del Pulmón

Estos estudios de la función pulmonar fueron realizados en 9 enfermos con afección pleural tratados por la decorticación. Tres operados poco después de la iniciación del hemotórax recobraron la función normal. Un enfermo con un hemotórax antiguo reveló mejoramiento funcional después de la decorticación, pero no retorno a lo normal.

Cinco pacientes con varias formas de pleuropatía tuberculosa fueron estudiados. Los que no tenían afección parenquimática observable y en los que la afección pleural había durado menos fueron los que mostraron mejores resultados funcionales. En un caso, se combinó la toracoplastia con la decorticación, dando por resultado dominio de la enfermedad pleural y parenquimática y función moderadamente buena. En un enfermo en que se combinó la decorticación con la lobectomía, el resultado clínico fué bueno, pero el funcional relativamente malo.

RESUME

La fonction pulmonaire après décortication du poumon

L'étude de la fonction pulmonaire pratiquée chez 9 malades atteints d'affection pleurale et traités par la décortication est rapportée. La fonction pulmonaire normale a été rétablie chez trois malades opérés précocement après l'apparition du hemothorax. Dans un cas de hemothorax déjà ancien la décortication a amélioré la fonction, mais n'a pas permis d'obtenir le retour à la normale.

Cinq malades présentant diverses formes d'affection tuberculeuse de la plèvre ont été étudiés. Chez ceux qui étaient indemnes de lésions parenchymateuses ou dont l'atteinte pleurale était parmi les plus récentes, les résultats fonctionnels obtenus ont été très bons. Dans un des cas, la thoracoplastie a été associée à la décortication, ce qui a permis à la fois, de contrôler l'affection pleurale et parenchymateuse et de rétablir la fonction pulmonaire a un degré modéré. Chez un malade traité par décortication et lobectomie, les résultats cliniques ont été bons du point de vue clinique mais pauvres du point de vue fonctionnel.

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SOLITARY LUNG TUMORS[1]

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(Received for publication October 30, 1950)

Two years ago Effler, Blades, and Marks (1) published a paper calling attention to the problem of solitary lung tumors. Twenty-four case histories were reviewed therein and the surgical observations tabulated. The selection of these cases was based on the following criteria: (*1*) the tumor was an unexpected roentgenographic discovery, (*2*) there were no related symptoms, and (*3*) attempts to establish diagnosis were ineffectual until surgery. The interesting pathologic diagnosis in this group, coupled with the uniformly benign postoperative convalescence of the patients, prompted the writers to recommend surgical intervention as the procedure of choice.

The term "solitary lung tumor" is applied herein to an asymptomatic, spherical density demonstrated in either lung field by roentgenographic examination. Such lesions found in patients who were examined because of cough, fever, weight loss, hemoptysis, or other suggestive symptoms are not included.

OBSERVATIONS

In the past year, 16 patients have been operated upon at the Cleveland Clinic for the removal of asymptomatic solitary lung tumors. The lesions were revealed either by a mass roentgenographic survey or during investigation of an unrelated complaint. In the latter case the term "solitary lung tumor" has been applied only if the subsequent tissue study proved that there was no relation between tumor and primary complaint. The essential clinical details and findings are presented in table 1.

The average age in this group is 50 years; the youngest patient was 28 and the eldest 66 years of age. There was no operative mortality in the group, but 2 patients had minor complications which delayed discharge from the hospital, and one has since died from metastatic bronchogenic carcinoma.

Of the entire group of 16, 6 patients had peripheral bronchogenic carcinoma. Another had a solitary metastatic hypernephroma; the primary tumor had been removed six years previously. In 8 patients the "tumors" were found to be localized tuberculous lesions of various degrees of chronicity. In one, a hamartoma of the lung was removed. In the entire group of 16, 2 lesions were found which appeared incapable of potential damage, the hamartoma and one fibrotic laminated tuberculoma.

COMMENT

In the series presented by Effler, Blades, and Marks, 4 lesions were considered malignant. As the age of their patients was considerably lower than in the pres-

[1] Presented before the Mississippi Valley Trudeau Society, Columbus, Ohio, September 23, 1950.

[2] From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

ent series, however, it is not surprising to observe an appreciable increase in the incidence of malignancy in the latter group. Every reasonable diagnostic aid must be utilized in the clinical management of the patient with a solitary pulmonary lesion. If the diagnosis is not thus established, the patient must be evaluated as a surgical candidate. The dangers of thoracotomy and excision of the lesions do not justify unnecessary procrastination when the patient is apparently healthy. The high incidence of unsuspected malignant lesions is, in itself,

TABLE 1

Tabulation of Clinical Findings

CASE NO.	AGE	PATHOLOGIC DIAGNOSIS	PROCEDURE	DATE	COMPLICATION
1	62	Bronchogenic carcinoma	Left pneumonectomy	1/ 5/49	0
2	37	Tuberculoma*	Direct excision	6/ 3/49	0
3	62	Tuberculoma	Direct excision	6/30/49	0
4	56	Tuberculosis	Segmental resection	6/30/49	Postoperative thrombophlebitis, mild
5	65	Bronchogenic carcinoma	Right middle lobectomy	7/10/49	Subcutaneous emphysema
6	45	Hamartoma	Left lower lobectomy	10/17/49	0
7	56	Bronchogenic carcinoma	Left lower lobectomy	11/28/49	0
8	66	Bronchogenic carcinoma	Left upper lobectomy	2/ 2/50	0
9	51	Tuberculosis	Segmental resection	2/27/50	0
10	44	Tuberculosis	Segmental resection	3/27/50	0
11	47	Bronchogenic carcinoma	Right upper lobectomy	5/19/50	0
12	64	Tuberculoma	Direct excision	5/22/50	0
13	38	Bronchogenic carcinoma	Left upper lobectomy	6/19/50	0
14	28	Tuberculosis	Direct excision	7/ 3/50	0
15	46	Metastatic hypernephroma†	Left lower lobectomy	8/28/50	0
16	45	Tuberculosis	Direct excision	9/10/50	0

* The term "tuberculoma" is used only in solid, laminated lesions; other "soft" lesions (e.g., blocked cavity) are grouped under the single term "tuberculosis."

† Primary tumor removed seven years ago.

a decisive factor; of the remaining "benign" lesions, the overwhelming preponderance will indicate manifestations of localized pulmonary tuberculosis. Understandably no patient can be benefited by retention of an unknown pulmonary mass; conversely, cumulative experience suggests advantage through removal.

The alternative to surgical therapy is clinical observation; unless an observed lesion diminishes in size, however, the clinical problem remains. The belief that tumors must show progressive alteration in shape and size is erroneous. Actively metastasizing neoplasms of the lung, breast, and other organs may demonstrate little change in gross appearance over a period of years. Patients so afflicted who

have died under careful clinical scrutiny present examples familiar to all physicians.

SUMMARY

Sixteen patients operated upon because of the roentgenographic finding of a solitary tumor have been reported. The uncertainty of an accurate preoperative diagnosis has been emphasized. It is believed that surgical intervention is the procedure of choice whenever a solitary lung tumor is demonstrated in a person in apparent health.

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BRONCHOGENIC CARCINOMA AS A DIFFERENTIAL DIAGNOSTIC PROBLEM IN PULMONARY DISEASE[1]

II. Carcinoma Arising from Major Bronchi Complicated by Secondary Infection

JOHN H. MOYER AND ALFRED J. ACKERMAN

(Received for publication July 5, 1950)

In a previous communication (1) the pathologic findings were correlated with roentgenographic and clinical manifestations of bronchogenic carcinomas which arise in the major bronchi but which are uncomplicated by secondary infection. Once infection is superimposed, the roentgenographic and clinical manifestations of bronchogenic carcinoma become altered in such a way as to bring into focus a completely new group of differential diagnostic possibilities. It is with the latter aspect of the subject of bronchial tumors that the present communication is concerned.

Progressive bronchostenosis is attended by secondary pulmonary infection which may occur even when the occlusion is not yet complete. The pulmonary parenchymal infection may develop as a direct result of either recurrent hemoptysis, which may account for the so-called "hemoptysis atelectasis," or intrabronchial stasis. When bronchial impingement becomes manifest, expectoration increases. The sputum, at first mucoid, becomes purulent as stagnation of secretions and secondary infection develop peripherally. Pneumonia, bronchiectasis, pulmonary abscess, or empyema frequently develop, any one of which may mask the underlying disease, bronchogenic carcinoma. An initial diagnosis of uncomplicated pneumonia or "influenza" based on the presence of chills, fever, chest pain, and productive cough has been quite common (2). Laboratory studies all too often help to confirm the original impression. Pneumonia peripheral to bronchial obstruction may be of variable extent and duration. It almost always responds to treatment with antimicrobial drugs, and frequently shows prompt and complete resolution. With its subsidence there may be no residual changes to suggest a bronchogenic tumor. The inflammatory process tends to recur, however, as soon as treatment directed toward combating the infection is discontinued. Recurrent pneumonia, or pneumonia which runs an atypical course, particularly when associated with recurrent hemoptysis, should always raise the question of carcinoma. The primary tumor in such cases may be quite small, and is usually located in a major bronchus. "Unresolved pneumonia" in the absence of reliable differential findings is now generally considered to be an indication for exploratory thoracotomy (3).

Bronchiectasis, as a result of bronchial obstruction and secondary infection, is observed in approximately 20 per cent of patients with bronchogenic carcinoma. The bronchiectasis may be so prominent that the correct diagnosis is obscured, particularly if the primary tumor is not easily demonstrable. Because

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signs of infection are the most outstanding in such cases and the hemoptysis is easily attributable to bronchiectases due to other causes, bronchoscopy and laminagraphy are occasionally delayed, and the neoplasm is permitted to progress without early recognition. Bronchography is also usually avoided in acute stages of the "infection" and so another diagnostic method is not fully utilized.

Acute Pneumonic-like Lesions

The following case illustrates the diagnostic difficulty in cases which exhibit chiefly signs and symptoms of recurrent small focal lobular pneumonia, not unlike those seen in bronchiectases.

Case 10. A 47-year-old white male was studied because of chronic cough, productive of purulent and blood-tinged sputum, shortness of breath, pain in the right chest, and loss of weight. Physical examination revealed no abnormalities except for scattered crepitant rales throughout both lungs. The temperature was 99.5°F. The leukocyte count was 13,000 per cu. mm. with a normal differential count. Numerous sputum examinations failed to demonstrate tubercle bacilli or neoplastic cells.

Roentgenographic examination of the chest at the time of admission revealed no evidence of pulmonary disease. Re-examination one week later showed a small infiltration in the right hilar area adjacent to which there was a small area of localized emphysema. There was also a more extensive area of peribronchial infiltration at the right base near the cardiophrenic angle and the costophrenic sinus. These findings were interpreted as indicative of bronchopneumonia, and the possibility of bronchiectases was considered.

The patient's physical condition failed to improve, although the infection subsided temporarily on antimicrobial therapy, only to recur. The presence of bronchogenic carcinoma was strongly suspected. Bronchoscopy, although advised, was not permitted by the patient.

Repeated roentgenographic examinations at frequent intervals over a six-month period revealed a resolution of the basal infiltration, but showed a recurring small patch of infiltration in the right hilar area which did not increase in size or density. An examination one week prior to the patient's death showed a small cavity with a fluid level at the site of the infiltration and disseminated nodular metastases in both lower lung fields. Postmortem examination disclosed a primary squamous cell carcinoma of the right upper lobe bronchus extending to the main stem bronchus, with an abscess in the upper lobe and multiple metastases to both lower lobes, pleura, liver, brain, and adrenals.

There seems to be little doubt that the clinical manifestations of infection which were observed initially and the pulmonary abscess which developed subsequently were due to partial occlusion of the affected bronchus. The local tumor ulcerated and resulted in hemoptysis of increasing severity. This was another contributory factor which accounted for the recurrent localized atelectasis which never involved a large bronchopulmonary segment, but probably accounted for the transient infiltration at the base. The extent of atelectasis and pneumonic infiltration may vary even in cases in which large segments of the lung are apparently involved. Because the size of opacities thus produced change considerably, they may be misinterpreted as evidence of an inflammatory disease alone. The change following the administration of antimicrobial drugs may be so prompt as to make the possibility of a tumor remote.

Another cause for partial re-aeration of an involved atelectatic lung, observed by the writers in a few instances, is the occurrence of sufficient necrosis of the

endobronchial tumor to result in a decrease in the bronchostenosis and re-establishment of partial patency of the involved bronchus. The following case demonstrated this variability of pulmonary opacities, and it emphasizes the difficulty in differentiating them from pneumonic infiltrations.

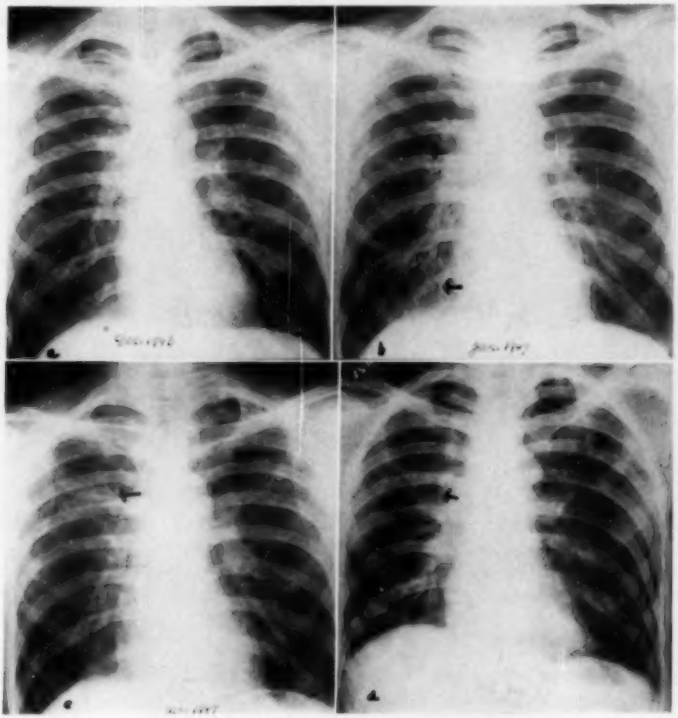

FIG. 10. Case 10. a. Admission roentgenogram; no evidence of disease.

b. One week after admission; a small patchy infiltration is seen in the right hilar area with adjacent localized emphysema; a patchy infiltration is also present at the right base.

c. Five months later; the infiltration in the right base has cleared but the one in the right hilar area has recurred and is now more marked.

d. Cavitation and dissemination have occurred.

Case 11. A 54-year-old white veteran was admitted because of cough, fever, and pain in the chest. Physical examination revealed dullness at the base of the left lung, rales, and bronchial breathing.

Roentgenographic examination of the chest showed a large irregular area of infiltration involving the left lower lobe. The left diaphragm was elevated and the heart and mediastinum were shifted to the homolateral side. A metastatic lesion destroying the second left rib was also noted. A diagnosis of bronchogenic carcinoma with skeletal metastases was made. Re-examination of the chest two days later showed a marked clearance of the

original density and only a triangular atelectatic segment near the lower left cardiac border. The heart and mediastinum returned to the midline. Bronchoscopy confirmed the fact that bronchial patency had again been established due to a sloughing of the tumor mass.

The above and other similar observations serve to emphasize that promptly resolving infiltrations do not always exclude the possibility of bronchogenic carcinoma. This is especially important in cases which exhibit no metastases to confirm a diagnosis of the neoplasm.

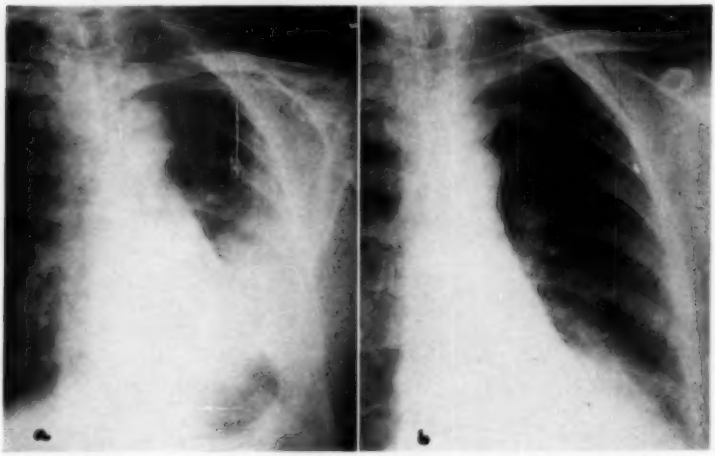

FIG. 11. Case 11. a. Opacity at left base suggesting atelectasis of left lower lobe.
b. Two days later. The atelectasis has been relieved due to necrosis of the tumor and temporary re-establishment of patency of the bronchial lumen.

Carcinoma Masquerading as Unresolved Pneumonia

Slowly resolving pneumonic infiltrations are at times difficult to differentiate from bronchogenic carcinoma. This is particularly true when the former disease fails to respond promptly to treatment. Pneumonias of this type are frequently associated with obstructive phenomena due to occlusion of larger bronchi by fibrinous or purulent exudate. Not infrequently, however, the causes for delayed resolution are not easily determined, as was true in the following case.

Case 12. A 50-year-old white male was admitted because of fever, cough, and hemoptysis of two months' duration. Sputum culture showed a mixed flora with no one species predominant.

Roentgenographic examination of the chest revealed an irregular area of infiltration in the right lower lobe which was considered to represent a pneumonia. The patient failed to improve after penicillin therapy. The pulmonary infiltration enlarged and interpretation of the roentgenograms suggested the possibility of tumor. Bronchoscopy and laminagraphy failed to demonstrate an endobronchial lesion. After two months the pulmonary infiltration resolved almost completely. Bronchography revealed an essentially normal bronchial tree. Subsequent follow-up examinations confirmed the original diagnosis of pneumonia.

In contrast to this satisfactory outcome in the above case, the following patient, who presented nearly identical manifestations, was found to have bronchogenic carcinoma.

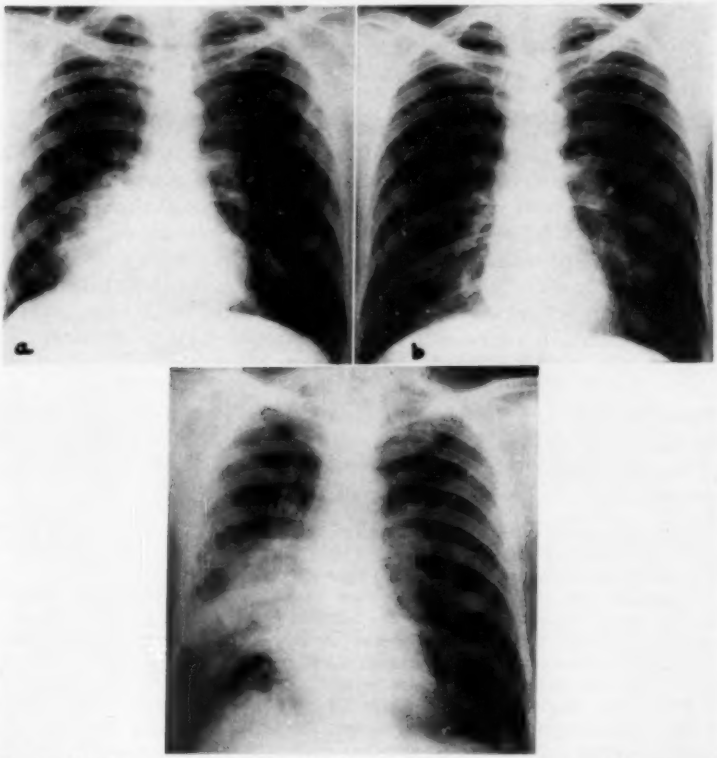

FIG. 12. Case 12. a. Infiltration in right lower lobe which was diagnosed "pneumonia." Because this did not resolve for a period of two months, despite antimicrobial therapy, malignancy was considered.

b. The infiltration has resolved.

FIG. 13. Case 13. (Bottom) Well-defined density in the right mid-lung field similar to Case 12 eventually proved to be bronchogenic carcinoma.

Case 13. A 69-year-old white male developed a nonproductive cough and an upper respiratory infection with fever four weeks prior to admission. He also complained of chest pain and intermittent dyspnea, which had grown progressively worse for the past five months. Physical examination revealed wheezing over the right base. The total leukocyte count was 13,000 per cu. mm. with a normal differential count.

Roentgenographic examination of the chest showed a large, fairly well defined density in the right mid-lung field adjacent to the hilum. From the periphery of its lateral margin

another smaller density extended toward the pleura at the axillary line. The right diaphragm was elevated. In the lateral view the density lay anteriorly, corresponding to the middle lobe. Planigrams showed a narrowing of the right bronchus near the orifice of the middle lobe bronchus. The findings were interpreted as consistent with the presence of bronchogenic carcinoma.

The patient was started on penicillin therapy following which he experienced subjective improvement. The temperature returned to normal and he gained ten pounds in weight. As soon as the acute symptoms subsided, a bronchoscopy was performed and the roentgenographic diagnosis was confirmed.

In considering the origin of pulmonary infiltrations, these cases illustrate rather well that little dependence can be placed on the roentgenographic appearance of these infiltrations. Although an infection accompanying pulmonary tumors may show marked resolution following antimicrobial therapy, some inflammatory lesions fail to respond to this form of treatment, and thus raise a suspicion of the presence of a tumor. Negative bronchoscopy in such cases frequently does not resolve the diagnostic problem since endobronchial tumors are so frequently beyond the range of the bronchoscope. In such cases, bronchography and laminagraphy may prove to be of superior value to bronchoscopy.

Parenchymal Invasion by Carcinoma Simulating Pneumonia

The advancement of a tumor within the lung modifies the signs of the bronchial obstruction, especially those caused by diminished lung volume (4). The lung may be expanded by the progressing tumor, and thus may resemble a pneumonic consolidation on the roentgenogram.

Case 14. A 47-year-old white male was admitted because of cough productive of moderate amounts of mucopurulent sputum, pain in the right chest, and dyspnea. Physical examination revealed signs of consolidation of the right upper lobe.

Roentgenographic examination of the chest showed an extensive infiltration of the upper lobe which was partly limited by the interlobar fissure. At that time a diagnosis of pneumonia was considered. The infiltration at first regressed slightly, but resolution failed to take place. Body-section roentgenography showed a marked stenosis of the right bronchus caused by a large tumor which extended also above the carina. In the peripheral portion of the upper lobe distal to the obstruction, there were several bronchiectatic areas and a ringlike cavity with tumor in its center. The tumor had extensively invaded the parenchyma. These findings were confirmed on post-mortem examination. The tumor had extended into the middle and lower lobes. The pleura was also invaded.

Tuberculosis and Bronchogenic Carcinoma

Tuberculous pneumonic infiltrations may occasionally offer diagnostic difficulties, especially when the clinical history is of a relatively short duration, the presenting symptom is hemoptysis, and sputum examinations fail to reveal tubercle bacilli. Ordinarily, however, the clinical course and repeated sputum examinations clarify the diagnostic problem without much delay.

Case 15. A 34-year-old white male was admitted because of gross hemoptysis, chronic cough, and malaise for one week prior to admission. Physical examination revealed signs of consolidation of the left upper lobe. The temperature was 100°F. Sputum studies were negative for *M. tuberculosis*.

Roentgenographic examination of the chest showed an area of consolidation involving the apex and subapical portion of the left upper lobe without a demonstrable cavity or infiltration elsewhere in the lung. Body-section roentgenograms showed a uniform soft tissue density in the same area. The left main and upper lobe bronchi were clearly demonstrated and were of normal width and patency. The apical ramifications of the upper lobe bronchus were also well demonstrated. In view of these findings, a diagnosis of an inflammatory disease was made, and tuberculosis was considered to be the most likely possibility. Five weeks after admission tubercle bacilli were cultured from gastric washings.

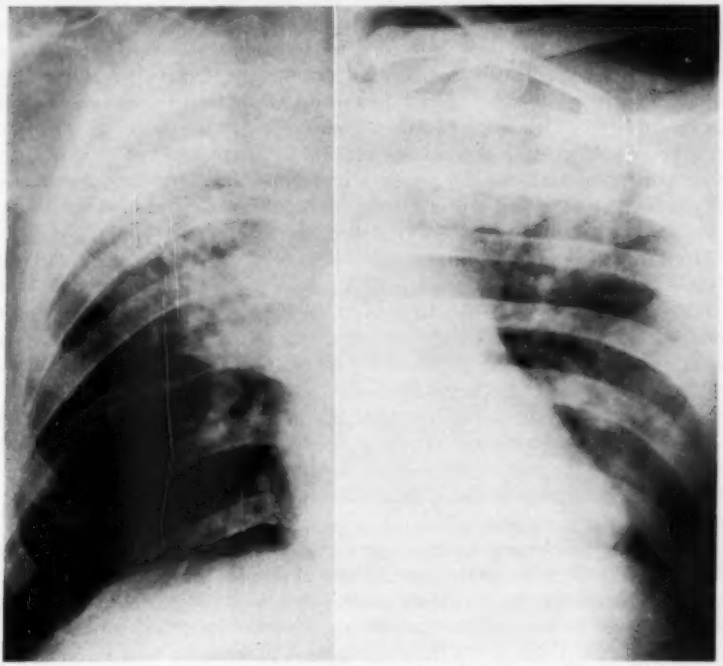

FIG. 14. Case 14 (Left). Extensive infiltration of the right upper lobe which is limited by the interlobar fissure. A diagnosis of pneumonia was erroneously made.

FIG. 15. Case 15. (Right) Extensive infiltration of left upper lobe due to tuberculosis. The character of the infiltration appears quite similar to that in case 14.

Cases of this type (Cases 14 and 15) serve to emphasize the value of body-section roentgenography. The conventional films may demonstrate only dense opacities without providing a clue to their underlying cause. The distinction between neoplastic infiltration and obstructive atelectasis is frequently impossible. The presence of atelectasis is deduced from the effects of the reduced pulmonary volume, but it is not distinguishable on the basis of a difference in density. In body-section roentgenograms such a distinction is possible. Greineder

(5) pointed out that the tumor almost invariably is denser than the atelectatic zone which surrounds it. The writers have found that this distinction is usually possible and of definite diagnostic significance. This "core shadow" of the carcinoma is usually rather sharply delineated and is observed in the vicinity of larger bronchi which are the site of origin of bronchogenic tumors. Visualization of the bronchi themselves is greatly facilitated by the peribronchial opacities due to tumor and atelectasis. The demonstration of the bronchial lumen is of great significance, particularly in the detection of bronchogenic carcinoma. Laminagraphy thus reveals alterations within the bronchi supplying the involved pulmonary segment and within their peripheral ramifications distal to the gross parenchymal lesion. The bronchus may assume the form of a narrow rigid channel, usually well within a peribronchially infiltrating tumor; or its lumen may be partly filled by polypoid tumor growing within the bronchus. The latter is more often observed in the large or main stem bronchi.

Constriction of the bronchial lumen, although a valuable finding, is not necessarily indicative of bronchogenic tumor. Marked degrees of stenosis may occur as a sequel to inflammatory diseases, especially tuberculosis (Case 5, (1)). The proliferative inflammatory changes and scars within the bronchial wall may produce irregularities of the lumen indistinguishable from neoplastic infiltrations of the bronchus. The conclusive diagnosis of neoplasm is based rather on the combination of the alterations of the bronchus and character of the adjacent pulmonary infiltration. In the presence of an inflammatory disease in which the pulmonary parenchyma is primarily involved and the bronchi spared, such as tuberculous or nontuberculous pneumonia, the bronchi are well outlined and show no evidence of stenosis or occlusion by intrabronchial changes. The bronchi distal to post-inflammatory stenosis are not infrequently dilated and the body section roentgenograms reveal isolated or multiple bronchiectases regardless of the etiology of the stenosis.

Occasionally pulmonary tuberculosis may obscure a coexistent bronchogenic carcinoma. This is particularly true in cases of chronic but progressive tuberculosis in which sputum examinations constantly reveal tubercle bacilli. Bronchostenosis due to endobronchial tuberculosis produces atelectasis similar to that caused by tumor (Case 5). As the displacement phenomena may be common to both diseases, the difficulty in diagnosing carcinoma in the presence of an already existent tuberculosis is increased. The following case provides an illustration of this problem.

Case 16. A 65-year-old white male was treated for ten years for pulmonary tuberculosis. The sputum was positive for tubercle bacilli. Serial roentgenographic examinations showed bilateral fibroproductive tuberculosis which progressed considerably in the right upper lobe over a period of two years. Prior to his last admission to the hospital, the patient's general condition deteriorated considerably. He developed a more severe cough, hemoptysis, dyspnea, low-grade fever, and weight loss.

Repeated roentgenographic examinations showed a homogeneous density of the right upper lobe and a homolateral displacement of the trachea. The inferior margin of the density was convex. This was thought to be due to parenchymal infiltration rather than atelectasis, which resulted in retraction of the affected lobe. A bronchoscopic examination was

nonrevealing. The patient died six months after this last admission. On post-mortem examination a bronchogenic carcinoma was found in the right upper lobe in addition to bilateral tuberculosis.

Pneumonitis Secondary to Bronchogenic Carcinoma versus Cardiac Failure with Thromboembolic Manifestations

In some instances obstructive atelectasis and the complicating pneumonic changes associated with carcinoma need to be differentiated from pulmonary emboli and the resulting infarction. The symptoms of dyspnea, hemoptysis, and chest pain usually present in the latter are not sufficiently specific or reliable to permit a definite diagnosis. Infarcts give rise to densities which in their locali-

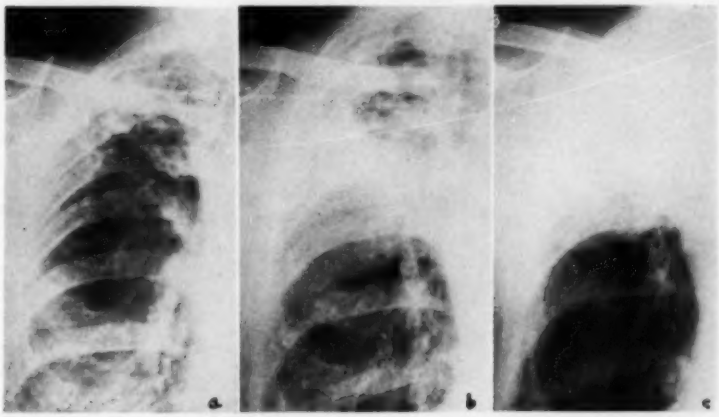

FIG. 16. Case 16. a. Chronic fibrocaseous tuberculosis of the right upper lobe.
b. The infiltration has extended. The sputum continues positive for tubercle bacilli.
c. Six months later. The infiltration has become very dense and homogeneous. Bronchogenic carcinoma is now present.

zation and distribution may resemble obstructive atelectasis, since the pulmonary vessels have the same anatomical distribution as the bronchi. Westermark (6, 7, 8) called attention to the fact that pulmonary infarcts, in contradistinction to obstructive atelectasis, do not cause a reduction in volume of the segment involved. In the writers' experience, the value of this differential sign is limited because of the infection which frequently accompanies the atelectasis, and thus prevents a reduction of volume commensurate with the degree of obstruction. It should also be borne in mind that isolated cases of pulmonary emboli do occur in patients who suffer, not only from bronchogenic carcinoma, but also from cardiovascular disease. Some of these problems are illustrated in the following cases.

Case 17. A 60-year-old white male was admitted with a fifteen-year history of asthma which had become more severe approximately six months prior to admission. A chronic cough

had recently become productive of mucoid sputum which on several occasions contained streaks of blood. Physical examination presented a temperature of 100°F., a pulse rate of 130 per minute, an enlarged heart with fibrillating auricles, peripheral edema, rales in the chest, and several enlarged cervical lymph nodes. Laboratory studies showed a normal erythrocyte and total leukocyte count. The erythrocyte sedimentation rate was 25 mm. per hour. The vital capacity was 28 per cent of normal.

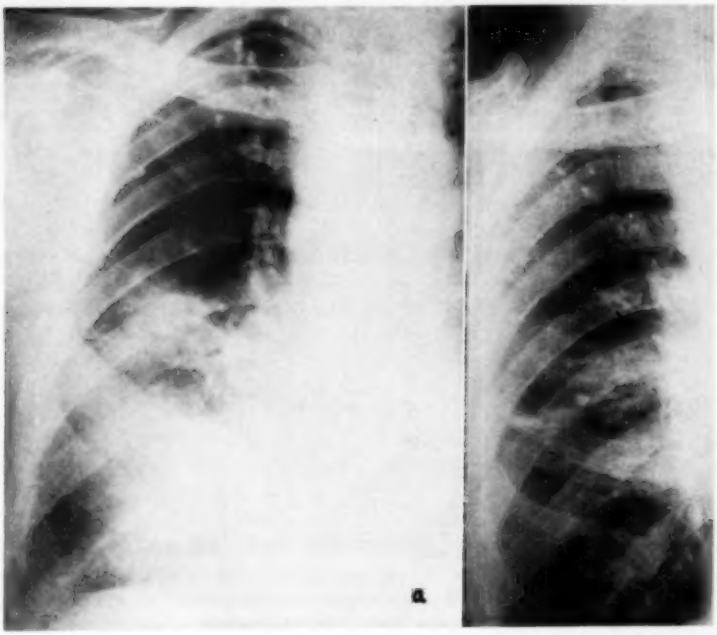

FIG. 17. Case 17. a. Confluent round area of increased density in the right lower lung field thought to be due to pulmonary infarction.

b. Two weeks later. Marked but incomplete resolution has occurred. This proved to be bronchogenic carcinoma.

Roentgenographic examination of the chest showed confluent round areas of increased density, with somewhat poorly defined margins in the right lower lung field and a generalized enlargement of the heart. These findings were interpreted as representing pulmonary emboli or infarcts secondary to cardiac failure.

The patient improved after digitalization. He also received penicillin, since it was believed that the clinical history indicated a chronic pulmonary infection. Repeated roentgenographic examination showed a prompt though incomplete resolution of the pulmonary infiltrations. A small area of increased density persisted in the hilar area. Although the patient no longer showed evidence of cardiac decompensation, the dyspnea became more severe. He again had an elevation of temperature and hemoptysis. In view of these clinical and roentgenographic findings, a diagnosis of bronchogenic carcinoma was made. Material obtained by biopsy of one of the cervical nodes showed evidence of a squamous cell carcinoma presumably originating in a bronchus. The patient died four months after admission

to the hospital. Post-mortem examination revealed a squamous cell carcinoma arising from the right lower lobe bronchus and multiple metastases to distant organs.

Case 18. A 48-year-old white veteran was admitted because of cough, dyspnea, and weakness for two years, with intermittent hemoptysis for two months. He had been treated for congestive heart failure. Physical examination revealed numerous moist rales at the bases of both lungs. The liver edge was palpable 4 cm. below the right costal margin. The heart was enlarged, and a grade II mitral systolic murmur was present. No peripheral edema was noted. The clinical diagnosis of cardiac failure seemed obvious.

FIG. 18. Case 18. Dense, well-circumscribed infiltration in the right base quite similar to that in Case 17. Bronchogenic carcinoma was considered, but one month later the chest was clear. The diagnosis was pulmonary infarction.

Roentgenographic examination of the chest revealed a large, round, rather sharply delineated density in the right lower lung field and a marked increase of the bronchovascular markings in the hilar area. There was only a slight congestion in the left hilar area. The heart was enlarged. The findings were interpreted as evidence of congestive heart failure with pulmonary infarction. The possibility was considered that bronchogenic carcinoma might be present. The patient responded satisfactorily to treatment except for continued hemoptysis. As this increased the possibility of pulmonary neoplasm, bronchoscopy was advised but no tumor was found. Re-examination one month later showed progressive absorption of the large infarct and disappearance of signs of passive congestion.

Although both patients had similar clinical symptoms at the time of admission and not dissimilar changes in the chest roentgenograms, in one patient the cardiac failure was responsible only for a part of the symptoms and signs. Broncho-

genic carcinoma was the ultimate cause of his death. The other patient had congestive heart failure with a pulmonary infarct. The prolonged hemoptysis in the latter instance warranted a clinical suspicion of bronchogenic tumor.

Bronchogenic Carcinoma Associated with Cavitation

Although cavities are frequently associated with bronchogenic carcinoma, they usually occur in late stages of the disease when other more definite signs of carcinoma are present. In some cases, however, evidence of "pulmonary abscess" is present on the initial examination when the clinical symptoms are of only short duration. Under these circumstances, tuberculosis and lung abscess become very important in the differential diagnostic considerations. The cavities associated with bronchogenic carcinoma are either an expression of infection complicating bronchial occlusion (Case 21), and thus represent true obstructive pulmonary abscesses; or they may occur within necrotizing portions of the parenchymal neoplasms (Case 23), in which instance the walls of the cavity are composed of tumor tissue. Not infrequently both factors, i.e., infection beyond the obstruction and tumor necrosis, play an equally important role. The abscess is frequently accompanied by fever, chills, chest pain, purulent sputum, and leukocytosis, as is the case with any lung abscess. As a consequence, the underlying pathologic process is frequently obscured. Occasionally the tumor mass may slough off and at least a transient bronchial patency may permit spontaneous drainage and temporary relief of symptoms.

It is only fair to state that the roentgenographic features of neoplastic cavities are frequently sufficiently distinct to permit a correct diagnosis. In many instances, however, the recognition of the basic disease depends on the clinical course. Body-section roentgenography is especially valuable in the recognition of cavities with their variable characteristics. It not only aids in visualization of cavities which are not demonstrated with sufficient clarity on conventional films, but also defines the contour and thickness of their walls. The relation of the cavity to the communicating bronchus is also of some significance. The appearance of the cavity depends on its pathological anatomy. Those which result from tumor necrosis are usually irregular in shape, the walls are thick, and show irregular scalloping most likely due to projection of tumor tissue into the lumen of such cavities. The communicating bronchus is most commonly constricted, and peribronchial infiltration accompanies the bronchus from the hilum to the cavity and often beyond it. Contrariwise, inflammatory cavities not associated with bronchial obstruction fail to demonstrate the infiltrations projecting into the lumen. They are either thin walled, frequently seen in chronic tuberculosis, or are surrounded by a rather homogeneous inflammatory zone, which may have a similar appearance in nontuberculous and tuberculous lesions. The communicating bronchus is usually not constricted. The differential diagnosis of cavitary lesions gains significance in the age group in which bronchogenic carcinoma occurs most frequently, particularly when the cavity is in a location less frequently involved in tuberculosis.

The following cases illustrate the points discussed above.

Case 19. A 34-year-old white male was admitted complaining of weight loss, fever, and persistent cough of six months' duration. On physical examination crepitant rales were found at the right base laterally and posteriorly.

Roentgenographic examination of the chest showed a fairly well defined parahilar infiltration on the right with a central cavity and a horizontal fluid level. An area of infiltration in the right cardiophrenic sinus was also present. Planigrams of the chest showed an oval cavity with a sharply delineated wall. The surrounding infiltration was of soft homogeneous density. There was no demonstrable constriction of the communicating bronchus.

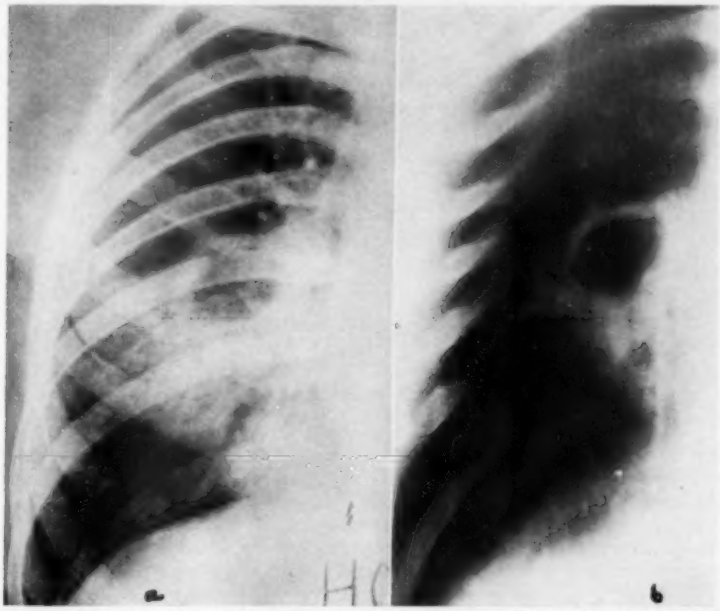

FIG. 19. Case 19. a. Parahilar infiltration, with cavitation and a horizontal fluid level due to tuberculosis.

b. Planigram showing a sharply delineated wall of the cavity with a homogeneous density surrounding it. There was no constriction of the communicating bronchus.

The roentgenographic findings were interpreted as consistent with pulmonary abscess or tuberculosis with spread to the lower lobe. Sputum examination and culture confirmed the diagnosis of tuberculosis.

Case 20. A 60-year-old white male was admitted complaining of chest pain, dyspnea, cough of four months' duration, and occasional hemoptysis during the last two weeks. Physical examination was noncontributory except for a few scattered crepitant rales near the left hilum posteriorly. Laboratory studies were nonrevealing.

Roentgenographic examination of the chest showed a fairly large, well-defined area of infiltration in the left hilar region with central cavitation and two horizontal fluid levels. These findings were interpreted as consistent with a pulmonary abscess. Laminagrams confirmed the findings on conventional films. In addition, the cavity walls were without

undulations and the surrounding parenchymal infiltration was homogeneous. There was no evidence of endobronchial disease. Bronchography added no additional information.

Bronchoscopic examination failed to disclose evidence of tumor. Nevertheless, the chronic nature of the disease, a poor response to penicillin, and lack of signs of an acute inflammatory disease suggested the possibility of a bronchogenic carcinoma. Consequently an exploratory thoracotomy and pneumonectomy were performed. Pathologic examination of the removed lung revealed a large pulmonary abscess without evidence of malignancy.

FIG. 20. Case 20. Chronic lung abscess showing well-defined area of infiltration with central cavitation in the left hilar region. The cavity walls are not scalloped, and are surrounded by homogeneous parenchymal infiltration.

Case 21. A 50-year-old white male was admitted because of weakness, hemoptysis, shortness of breath, cough productive of mucopurulent sputum, and weight loss for the past three months. The patient had been bronchoscoped shortly after the onset of his illness, but apparently no disease was found. Physical examination revealed a chronically ill patient with signs of consolidation over the left upper lobe of the lung.

Roentgenographic examination of the chest showed a large infiltration extending from the left hilum into the periphery of the upper lobe. There was a cavity in the first intercostal space. The left diaphragm was elevated. Body-section roentgenograms showed a marked stenosis of the left upper lobe bronchus by a tumor mass growing around the bronchus. In the periphery of the stenosed bronchus there was a fairly large irregular cavity, the walls of which suggested neoplastic infiltration. Bronchography confirmed the findings of bronchostenosis, consistent with neoplasm.

Bronchoscopy revealed a fixed and narrowed left upper lobe bronchus. Examination of biopsy material from this area showed only chronic inflammatory tissues. The diagnosis of

bronchogenic carcinoma (squamous cell), which occluded almost completely the left upper lobe bronchus, was confirmed at surgery.

The different roentgenographic characteristics associated with pulmonary cavitation from different causes are quite important considerations. If they are not evaluated in the light of all available collateral findings, however, erroneous conclusions frequently may be drawn. This is particularly true if the cavitation is due to primary necrosis of a neoplasm. The occasional case of this type may show thin-walled cavities without evidence of bronchial involvement, thus resembling tuberculosis or acute lung abscess due to other causes. This is most frequently noted with metastatic lesions. The following cases exemplify these points.

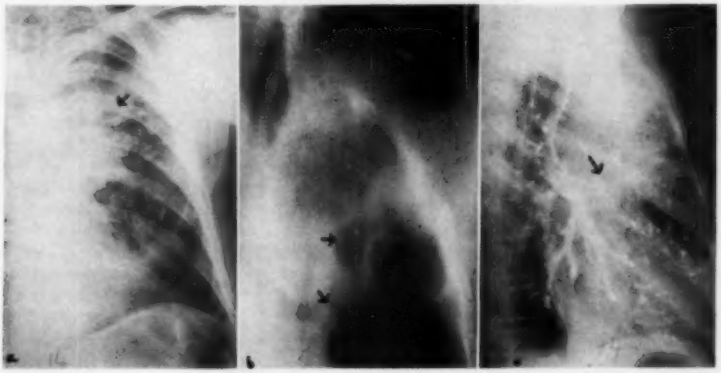

FIG. 21. Case 21. a. Infiltration extending from left hilum to the periphery of the upper lobe. A cavity was noted under the second rib.

b. Planigram showing tumor mass which is occluding the upper lobe bronchus. A large cavity is readily visualized with an irregularly scalloped wall suggesting neoplasm.

c. Bronchogram. The upper lobe bronchus is occluded.

Case 22. A 47-year-old white male was admitted because of cough productive of mucopurulent sputum, hemoptysis, weakness, and pain in the right hip. Physical examination was noncontributory. Sputum studies for tuberculosis were negative.

Roentgenographic examination of the chest showed a fairly large, thin-walled cavity containing a small amount of fluid situated in the right lower lung field. No definite evidence of mediastinal adenopathy was found. The diaphragm was normal. Roentgenographic examination of the pelvis showed virtually complete dissolution of the right ischium, consistent with a metastatic carcinoma.

It is apparent that the roentgenographic features of the cavity in this case in no way suggested bronchogenic carcinoma. The lesion was distinctly limited; the wall of the cavity was thin, not unlike that in pulmonary tuberculosis; the adjacent parenchyma was free from disease. The diagnosis was established on the basis of secondary skeletal metastases. Pathological examination revealed primary necrosis of the tumor mass.

FIG. 22. Case 22. Thin-walled cavity containing fluid. The cavity in this case was due to primary necrosis of the tumor and not a result of bronchial obstruction or secondary infection.

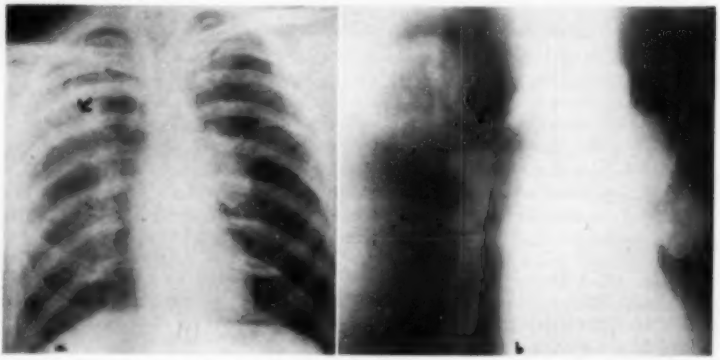

FIG. 23. Case 23. a. Admission roentgenogram showing infraclavicular cavitation. Contralateral hilar adenopathy is present.

b. Planigram showing thick and somewhat scalloped wall of the cavity which suggests neoplasm, although the bronchus is not obstructed. This was found to be a metastatic lesion from bronchogenic carcinoma of the left upper lobe.

Case 23. A 51-year-old white male was admitted complaining of right chest pain, dry cough, weight loss, dyspnea, and intractable hiccoughing. Physical examination revealed numerous

musical rales over the right upper thorax posteriorly. Neurological examination was negative. Laboratory studies, including sputum examinations for tuberculosis, pathogenic organisms, and tumor cells, were negative.

Roentgenographic examination of the chest showed an ill-defined, ringlike infiltration in the right infraclavicular region, with a fairly thick, slightly scalloped wall. There was no evidence of a fluid level and the remaining pulmonary parenchyma was normal. There were enlarged nodes in the left hilum, although none were seen in the right. Planigrams of the chest showed a thick-walled cavity with an irregular lumen due to variable extension of the mural infiltration into the lumen of the cavity. The communicating bronchus was well demonstrated in several sections, and showed no evidence of bronchial occlusion or constriction.

The interpretation of these findings seemed difficult because of the limited peripheral parenchymal disease with a "dry" cavity and contralateral mediastinal adenopathy. Tuberculosis was considered, since in this disease the extent of adenopathy may vary as well as the site of lymphatic involvement. Coccidioidomycosis is known to produce chronic indolent cavities, but the writers have not seen contralateral adenopathy associated with the localized chronic form of this disease. Bronchogenic carcinoma was seriously considered and bronchoscopy was performed, but no evidence of tumor was detected. Examination of material from biopsies of palpable cervical and axillary nodes was also negative. Thoracotomy was not thought to be indicated because of the contralateral adenopathy. The patient had a sudden severe and fatal hemoptysis after admission to the hospital.

Post-mortem examination showed that the lumen of the left upper lobe bronchus was markedly occluded by the tumor mass and was almost completely obliterated. This primary site had not previously been suspected. In the right upper lobe a thin-walled cavity measuring 4 cm. in diameter was found, composed entirely of tumor tissue without evidence of infection. A lymphangitic spread was noted throughout both lungs. The hilar lymph nodes were extensively involved by tumor.

This case demonstrates very vividly the protean character of the disease. A subapical cavity at the time of initial examination suggested the possibility of a chronic inflammatory disease, especially since there was no evidence of bronchial obstruction. Actually it represented a necrotizing metastatic lesion which was present before the primary tumor originating in the left bronchus could be recognized. The failure of bronchoscopy to reveal the primary bronchogenic tumor only added to the confusion of the already bizarre clinical picture.

SUMMARY

The manifestations of bronchogenic carcinoma complicated by bronchostenosis and secondary infection have been considered in respect to the approach to some of the differential diagnostic problems which are presented.

Inflammatory processes distal to endobronchial neoplasms usually respond to antimicrobial therapy, but are prone to relapse as soon as therapy is discontinued. The occurrence of this phenomenon should raise the question of carcinoma, particularly when encountered in the older age group. The demonstration of bronchiectasis does not exclude the possibility of carcinoma since bronchial dilatation distal to the obstruction is a frequent occurrence.

Unresolved pneumonia and residual fibrosis may resemble carcinoma. The results of laminagraphy, bronchography, and bronchoscopy usually permit a conclusion as to the exact nature of the process. When the question remains in doubt, however, an exploratory thoracotomy is indicated.

Parenchymal invasion by the tumor mass frequently modifies the signs of atelectasis, especially those caused by decreased lung volume. The roentgenographic picture may then resemble pneumonic consolidation. Frequently a differentiation is possible only by laminagraphic study of the infiltration and its relationship to the communicating bronchus.

By roentgenographic studies a distinction also can be made between simple inflammatory disease and atelectasis or pneumonitis secondary to endobronchial disease. The demonstration of the bronchial lumen and its relationship to the adjacent pulmonary infiltration is of value in reaching a conclusive diagnosis.

Pulmonary thromboembolic disease may resemble atelectasis resulting from bronchogenic carcinoma since the pulmonary vessels follow the same distribution as the bronchi. Both of these processes have been noted concurrently in the same individual.

Cavities associated with bronchogenic carcinoma may either be a result of infection complicating the bronchial occlusion or they may occur within necrotizing portions of the pulmonary neoplasm. Body-section roentgenography is especially valuable in the recognition and identification of cavities. It also defines the contour and thickness of their walls and their relationship to the communicating bronchus. The significance and reliability of these observations in differentiating cavities due to other causes have been discussed.

SUMARIO

El Carcinoma Broncógeno como Problema de Diagnóstico Diferencial en la Tuberculosis Pulmonar: II. Carcinoma Originado en los Bronquios Mayores y Complicado por Infección Secundaria

Considéranse aquí las manifestaciones del carcinoma broncógeno complicado por estenosis bronquial e infección secundaria con respecto a la manera de abordar algunod de los problemas de diagnóstico diferencial que plantea dicho estado.

Los procesos inflamatorios distales a las neoplasias endobronquiales suelen responder a la antibióticoterapia, pero sobreviene una recidiva apenas se suspende la terapéutica. Esto debe suscitar la idea de carcinoma, sobre todo en personas de cierta edad. Un hallazgo de bronquiectasia no excluye el carcinoma, pues frecuentemente existe dilatación bronquial distal a la oclusión.

La neumonía irresuelta y la fibrosis residual pueden semejar carcinoma. La laminagrafía, la broncografía y la broncoscopia permiten por lo general llegar a una conclusión acerca de la naturaleza exacta del proceso, pero si no sucede así, hállase indicada una toracotomía exploradora.

La invasión del parénquima por la tumefacción modifica frecuentemente los signos de atelectasia, máxime los ocasionados por la disminución del volumen pulmonar. El cuadro roentgenológico puede simular hepatización. A menudo sólo resulta posible la diferenciación por el estudio laminagráfico de la infiltración y de la relación del bronquio interesado con la misma.

Por los estudios roentgenológicos cabe trazar una distinción entre la enferme-

dad inflamatoria simple y la atelectasia o neumonitis secundarias a afección endobronquial. El descubrimiento de la luz del bronquio y de su relación con la adyacente infiltración pulmonar resulta útil para llegar a un diagnóstico terminante.

Una tromboembolia pulmonar puede semejar atelectasia debida a carcinoma broncógeno, visto que los vasos pulmonares siguen el mismo trayecto que los bronquios. Ambos procesos han sido notados concurrentemente en el mismo individuo.

Las cavernas asociadas con el carcinoma broncógeno pueden bien ser efecto de la infección que complica la oclusión bronquial o sobrevenir dentro de las porciones esfaceladas de la neoplasia pulmonar. La planigrafía resulta en particular valiosa para el reconocimiento e identificación de las cavernas. También define el contorno y el espesor de las paredes de las mismas y su relación con el bronquio interesado. Discútense la importancia y la fidedignidad de estas observaciones para diferenciar cavernas debidas o otras causas.

RESUME

Cancer bronchiogénique en relation avec le problème du diagnostic différentiel en tuberculose pulmonaire: II. Cancer primitif d'une bronche souche compliqué d'infection secondaire

Les manifestations du cancer bronchiogénique compliqué de sténose bronchique et d'infection secondaire ont été considérées sous l'angle des problèmes de diagnostic différentiel qui sont présentés.

Le processus inflammatoire distal lié au néoplasme endobronchique cède habituellement à la thérapie antibiotique; toutefois il reprend quand le traitement cesse. Ce phénomène permet d'envisager le diagnostic de cancer, en particulier chez les sujets agés. La découverte d'une dilatation bronchique n'exclut pas le cancer car l'obstruction bronchique s'accompagne souvent d'une dilatation distale.

La pneumonie dont la résolution est incomplète avec présence de tissu fibreux résiduel peut simuler le cancer. La tomographie, la bronchographie et la bronchoscopie permettent, en général, de parvenir à une conclusion quant à la nature du processus. Toutefois, quand ceci n'est pas possible, une thoracotomie exploratrice s'impose.

L'invasion du parenchyme par la masse néoplasique modifie souvent les signes d'atélectasie, en particulier ceux qui sont liés à une réduction de volume du poumon. L'image radiologique peut alors ressembler à celle de l'hépatisation du poumon. Il arrive souvent que la différenciation ne soit possible qu'après une étude tomographique de la région infiltrée et de ses rapports avec la bronche qui l'alimente.

L'étude radiologique permet également de distinguer l'affection inflammatoire simple de l'actélectasie ou de la pneumonie secondaire à une affection endobronchique. L'examen de la lumière bronchique et de ses rapports avec le territoire pulmonaire infiltré est important pour parvenir à un diagnostic concluant.

La thrombo-embolie pulmonaire peut ressembler à l'atélectasie produite par le cancer bronchiogénique en raison de la similitude de répartition des vaisseaux pulmonaires et des bronches. Ces deux processus ont été constatés chez un même individu.

Les cavernes en relation avec le cancer bronchiogénique peuvent être déterminées par une infection secondaire à l'oblitération bronchique, ou se produire dans les masses cancéreuses nécrotiques du tissu pulmonaire cancérisé. La radiographie tomographique est particulièrement utile pour déceler et identifier ces cavités. Elle permet également de définir le contour et l'épaisseur de leur parois, ainsi que leurs rapports avec la bronche qui les alimente. La signification et la valeur de ces observations pour la différenciation de cavités d'étiologies diverses ont été discutées.

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INTERMITTENT STREPTOMYCIN REGIMENS

An Analysis of Ninety-seven Patients with Pulmonary Tuberculosis Treated with One or Two Grams of Streptomycin Every Third Day

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INTRODUCTION

As pulmonary tuberculosis is a disease prone to exacerbations and chronicity, longer courses of streptomycin therapy seem desirable, especially in the management of recent disease. Such a prolongation of the effective suppressive action of streptomycin on *M. tuberculosis* admittedly is not supplied by shortening the treatment periods in an effort to avoid the emergence of drug-resistant strains of tubercle bacilli. Since the initial use of streptomycin in the treatment of pulmonary tuberculosis, however, the trends toward decreased daily dosage and less frequent injections (1, 2, 3, 4) have demonstrated that this drug is effective over a wide range of time-dose relationships. Moreover, animal experiments (1, 4, 5) have further demonstrated that the antituberculous activity of streptomycin in guinea pigs is sustained and not appreciably diminished by inoculations on alternate days or weeks.

In a previous study of the effects of streptomycin administered intermittently to 16 patients with pulmonary tuberculosis (6), the results were in apparent agreement with these impressions, and, in addition, revealed a strikingly low incidence of drug-resistant strains of *M. tuberculosis*. These patients, who received 2 gm. of intramuscular streptomycin every third, or every fourth, or every fifth day, exhibited clinical and roentgenographic response considered comparable to that obtained on previous regimens. Furthermore, subjective evidence of streptomycin toxicity was not noted in a single case. Sputum "conversions" occurred in 8 patients and, of the remaining 8 patients who continued to discharge tubercle bacilli, drug-resistant microorganisms were cultured from only one. The resultant decreased incidence of drug toxicity, the favorable clinical and roentgenographic response, and the number of sputum "conversions" indicated that the method of streptomycin administration was effective. Since further streptomycin is usually ineffective following the emergence to predominance of drug-resistant tubercle bacilli (3, 7, 8, 9), the striking observation that bacterial sensitivity was prolonged in this study suggested that there were numerous advantages to the regimen (6).

In an effort to validate or invalidate these original impressions, a larger study of the intermittent administration of streptomycin has been completed in 97 patients. Since it is imperative that therapeutic response be not sacrificed in order to prolong bacterial sensitivity, the results from this study are presented in detail so that all of the factors involved may be clearly set forth and the efficacy of this method of treatment evaluated.

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PLAN OF INVESTIGATION

The present study, preliminary reports of which have been presented elsewhere (10, 11, 12), was conducted during the period from April 1948 to July 1949. Observations were made on 97 patients with pulmonary tuberculosis, 49 of whom received 2 gm. of streptomycin in four divided doses every third day, and 48 of whom received 1 gm. in two divided doses every third day. The duration of a course of streptomycin therapy varied from a minimum of 126 days to a maximum of 189 days, depending upon response to therapy, time of sputum "conversion to negative," and results of serial streptomycin sensitivity studies. Streptomycin therapy was usually discontinued following the 126-day course if the streptomycin sensitivity studies revealed the presence of drug-resistant tubercle bacilli or if the patient had "converted to negative." If the welfare of the patients was not prejudiced, collapse procedures were withheld during the first 126 days. The patients were maintained on strict bed rest before, during, and after treatment. In addition, cod-liver oil cocktails, multivitamins, and 300 mg. of ascorbic acid were administered daily.

The pathologic character of the lesions and the age groups of the patients studied were extremely varied. The patients were not selected except to include an adequate number whose sputum was most likely to remain positive for tubercle bacilli throughout and after streptomycin therapy, so that streptomycin sensitivity studies might be accomplished. Whenever feasible, patients were observed for a period of at least one month prior to initiation of streptomycin therapy, so that a trend could be determined. Bronchoscopy was performed on each patient before therapy and at six-week intervals thereafter if endobronchial disease was present. Caloric vestibular function studies were performed on each patient before and after therapy and when otherwise indicated.

Materials and Methods

The patients were studied clinically by three of the writers, and the sensitivity studies were made by the fourth (W. E. D.). Clinical evaluations were made daily. The average amount of cough, sputum quantity and quality, body weight, and streptomycin toxicity were recorded at three-week intervals. Temperature and pulse rate were recorded five times daily.

Roentgenographic studies were made throughout the period of observation as follows: (*1*) stereoscopic views before treatment, on initiation and completion of therapy, and at three-week intervals throughout hospitalization; and (*2*) special films when indicated. Complete blood counts, erythrocyte sedimentation rates (Wintrobe), and urinalyses were obtained at three-week intervals. Sputum or gastric specimens were collected from each patient for culture two to four times weekly. These specimens were concentrated by the trisodium phosphate method (16), smeared, and approximately 0.1 ml. of the concentrated sediment inoculated on one tube of Petragnani's medium. Cultures were incubated at 37°C. and examined weekly, an average of four weeks being required for growth to occur on this medium. Cultures showing no visible growth after seven weeks' incubation were discarded as negative.

Streptomycin sensitivity studies, using the method recommended by the Laboratory Committee of the Sixth Streptomycin Conference (13), were made on solid media on all positive cultures. The outstanding advantage of solid media for sensitivity determinations

is that, by inference, the presence of sensitive organisms in the culture is shown. In contrast, methods using liquid media show only the presence of a sufficient number of resistant variants to produce growth after a given time interval, while the large majority of the population can still be sensitive to the concentration of streptomycin tested.

The following criteria are listed since it is important to define terminology used to express bacteriologic status:

Sensitive culture: Less than 4 plus growth on 10 γ per ml. tube. A patient must have had a sensitive culture before *and* after, *or on* a given date to be called sensitive at that time.

Resistant culture: 4 plus growth on 10 γ per ml. tube. A patient must have had a resistant culture before *and* after *or on* a given date to be called resistant at that time.

Unknown sensitivity: Sensitivity of organisms not determined because (a) the evaluation date fell between the last sensitive and the first resistant culture, (b) the evaluation date fell between the last resistant and the first sensitive culture thereafter, or (c) the evaluation date fell between the last sensitive culture and the conversion date which was marked by a positive culture on which sensitivity was not obtained.

"Converted:" No patient was designated as "converted" unless repeated cultures were negative for three months. For the 126-day evaluation, patients were called "converted" if negative cultures were reported prior to 126 days and subsequent cultures remained negative for three months.

Per cent resistant: Total number of patients with known resistant cultures multiplied by 100, divided by the total number of patients with positive cultures at the time of evaluation.

Per cent sensitive: Total number of patients with known sensitive cultures multiplied by 100, divided by the total number of patients with positive cultures at time of evaluation.

Per cent unknown: Total number of patients with unknown sensitivity multiplied by 100, divided by the total number of patients with positive cultures at time of evaluation.

Total number of patients analyzed: Number of patients with positive cultures plus number of patients converted.

Per cent "converted:" Total number of patients "converted" multiplied by 100, divided by total number of patients analyzed.

OBSERVATIONS

The study was divided into patients with far and moderately advanced pulmonary tuberculosis. A comparison of the results obtained from the administration of 1 and 2 gm. of streptomycin every third day necessitated a subdivision of these two groups. The groups and their abbreviations are as follows:

	Number of Cases	
Far advanced, 2 gm. (FA-2)	30	
Far advanced, 1 gm. (FA-1)	31	
Far advanced, 1 and 2 gm. combined (FA-C)		61
Moderately advanced, 2 gm. (MA-2)	19	
Moderately advanced, 1 gm. (MA-1)	17	
Moderately advanced, 1 and 2 gm. combined (MA-C)		36
Total number of cases in study		97

The variables of pathology, age, onset of disease, race, and complications are not expressed in the above groupings but may be seen in table 1[1]. To facilitate evaluation, the confluent and patchy pneumonic categories will be termed "new disease," and the other types of lesion, "old disease."

[1] The authors will furnish an individual analysis chart of the 97 patients upon request.

An imbalance of case distribution according to treatment regimen and extent of disease is noted in the pathologic groupings. The FA-2, FA-1, MA-2, and MA-1 series include 14 (46.6 per cent), 27 (87.0 per cent), 10 (52.6 per cent), and 2 (11.7 per cent) patients, respectively, with old disease.

The series was divided into age groups of less than 30 years and of 30 years or more. The FA-2, FA-1, MA-2, and MA-1 groups contained 9 (30.0 per cent), 21 (67.7 per cent), 6 (31.6 per cent), and 7 (41.2 per cent) patients, respectively, from the older age category.

An analysis of time of onset of disease shows a similar imbalance of distribution of the patients with an onset of six months or more.

The study included 16 (16.5 per cent) Negro patients; their distributions by treatment regimen and extent of disease were not significantly different from those of the other patients.

The 47 complications occurring prior to, and during, therapy were analyzed as tuberculous and nontuberculous lesions. The 42 tuberculous complications included 23 patients with recent hemorrhages, 13 with endobronchial lesions, 5 with pleural effusions, and one with a tuberculous sinus. The 5 nontuberculous complications included 3 patients with bronchiectasis and 2 with asthma.

These differences introduce additional variables which must be considered in future evaluations.

Clinical Course

The clinical course of the infection was evaluated in terms of temperature, sputum quantity, cough, body weight, and erythrocyte sedimentation rate. Of the 40 patients febrile at initiation of therapy, 27 (67.5 per cent) and 36 (90.0 per cent) were afebrile at completion of 21 and 126 days of streptomycin therapy, respectively. Of the 45 patients with a sputum volume of more than 30 cc. at initiation of streptomycin therapy, all but 9 were discharging 30 cc. or less at some time within 126 days. Analysis of these 9 patients reveals that one had silicotuberculosis, one had bronchiectasis, and the remaining 7 were in the older age group and had predominantly fibrocavernous disease. Seven of the 67 patients with a moderate or severe cough at initiation of treatment continued to have such a cough throughout 126 days of streptomycin therapy. All had fibrocavernous disease of long duration except one who had patchy pneumonic disease complicated by bronchiectasis. After 126 days of treatment, 51 (52.5 per cent) of the patients had gained ten or more pounds of body weight. At this same period, the erythrocyte sedimentation rate had returned to normal in 43 (44.3 per cent) patients.

Fever, sputum quantity, and cough usually improved most rapidly during the first forty-two days of therapy. After the forty-second day, the status of most patients continued to improve; in some, improvement was followed by relapse, and in a few, no remarkable improvement was ever noted.

It became necessary to analyze the course of illness in those patients whose disease showed little or no improvement attributable to streptomycin. Therefore, the following criteria were established for a poor clinical streptomycin result:

(*1*) In order for the disease to be designated as "stationary," the patients must have had a moderate or severe cough, a sputum quantity of more than 30 cc., a fever, *or* a loss of ten pounds of weight throughout 126 days of therapy.

(*2*) In order to be designated "improved with relapse," the patient had to improve to slight cough, sputum quantity of 30 cc. or less, no fever, *and* no loss of weight. Subsequently, he had to suffer a recurrence in *one* or more of the categories mentioned.

TABLE 1

Distribution of Cases by Type of Lesion and by Streptomycin Regimen

REGIMEN			FA-2	FA-1	FA-C	MA-2	MA-1	MA-C
Total number of cases			30	31	61	19	17	36
Number of cases classified by type of lesion	New disease	Confluent pneumonic	4	2	6	0	0	0
		Patchy pneumonic	12	2	14	9	15	24
	Old disease	Fibrocavernous with patchy pneumonic	6	19	25	5	1	6
		Fibrocavernous	7	3	10	4	1	5
		Chronic productive	1	1	2	1	0	1
		Silicotuberculosis	0	4	4	0	0	0
Age		More than 30 years	9	21	30	6	7	13
		Less than 30 years	21	10	31	13	10	23
Onset		Six months and longer	8	19	27	11	6	17
		Less than six months	22	12	34	8	11	19
Race		Negro	6	5	11	3	2	5
		White	24	26	50	16	15	31
Complications		Tuberculous	10	14	24	13	5	18
		Nontuberculous	1	2	3	0	2	2

FA-2 = Far advanced, 2 gm.
FA-1 = Far advanced, 1 gm.
FA-C = Far advanced, 1 and 2 gm. combined.
MA-2 = Moderately advanced, 2 gm.
MA-1 = Moderately advanced, 1 gm.
MA-C = Moderately advanced, 1 and 2 gm. combined.

Using this method of defining "poor clinical result," 18 (18.5 per cent) of the 97 patients studied were graded "stationary," and 6 (6.2 per cent), "improved with relapse." Of these 24 patients with poor clinical response, 20 (83.3 per cent) were in the far advanced groups, 18 (75.0 per cent) had fibrocavernous or fibrocavernous with patchy pneumonic disease, 19 (79.1 per cent) had their disease for six months or more, 20 (83.3 per cent) were 30 or more years of age, and 10 (41.7 per cent) were discharging drug-resistant tubercle bacilli within 126 days of the start of therapy. Thus the most common factors associated with poor clinical response are increased extent and chronicity of the disease and, to a lesser degree, the development of bacterial resistance.

In summary, 75 (75.3 per cent) of the patients showed clinical improvement. This response compares favorably with the clinical course of patients treated on the daily dosage schedules previously used on this service (14).

Complications

The tuberculous complications previously described responded well to intermittent streptomycin therapy. Serial bronchoscopies performed on the 13 patients with endobronchial tuberculosis showed complete recession of the lesions in all but one before completion of 126 days of therapy. In most instances complete recession, as evidenced by bronchoscopy, had already occurred following six weeks of therapy. One patient who failed to show such improvement had extensive silicotuberculosis, no sputum "conversion," and a poor over-all response to treatment. One patient with a tuberculous sinus had a prompt and complete healing of the lesion prior to completion of the 126 days of therapy.

The objective evidence of healing of the tuberculous complications observed in this study confirms the previous impression of the therapeutic efficacy of intermittent streptomycin regimens (6).

Streptomycin Toxicity

The 97 patients in the series were studied with serial caloric vestibular function tests and observed for signs and symptoms of other manifestations of streptomycin toxicity. Only one patient exhibited evidence of streptomycin toxicity prior to completion of 126 days of treatment. This patient, an eighty-pound, 53-year-old, white male, had mild transient vestibular dysfunction on approximately the hundredth day of treatment. Streptomycin therapy was continued, however, and his vestibular function returned to normal following completion of 126 days of treatment. Two patients who received 189 days of streptomycin therapy developed minor erythematous skin rashes after 153 and 165 days of therapy, respectively. In both instances, the eruptions were readily controlled by antihistaminics and were not of sufficient severity to merit the discontinuance of streptomycin.

In summary, the incidence of streptomycin toxicity was 1.03 and 5.0 per cent at the completion of 126- and 189-day courses of intermittent streptomycin therapy, respectively. This substantiates the previous observation (6) that the incidence of streptomycin toxicity is greatly reduced by regimens of intermittent therapy.

Roentgenographic Changes

Roentgenographic evaluations for group analysis were made at 0, 42, 84, 126, and 189 days. Roentgenographic changes were designated as *progressive*, *no change*, or *regressive*. The regressive changes were subdivided into minimal, moderate, excellent, and marked. *Minimal regression* was defined as the least possible significant change for the better, and *marked regression* as complete roentgenographic clearing of all infiltrations. *Moderate* and *excellent regression* represent proportionate intermediary regressive changes. No roentgenogram was evaluated after thoracoplasty was performed. Examples of these designations of roentgenographic changes may be seen in figure 1.

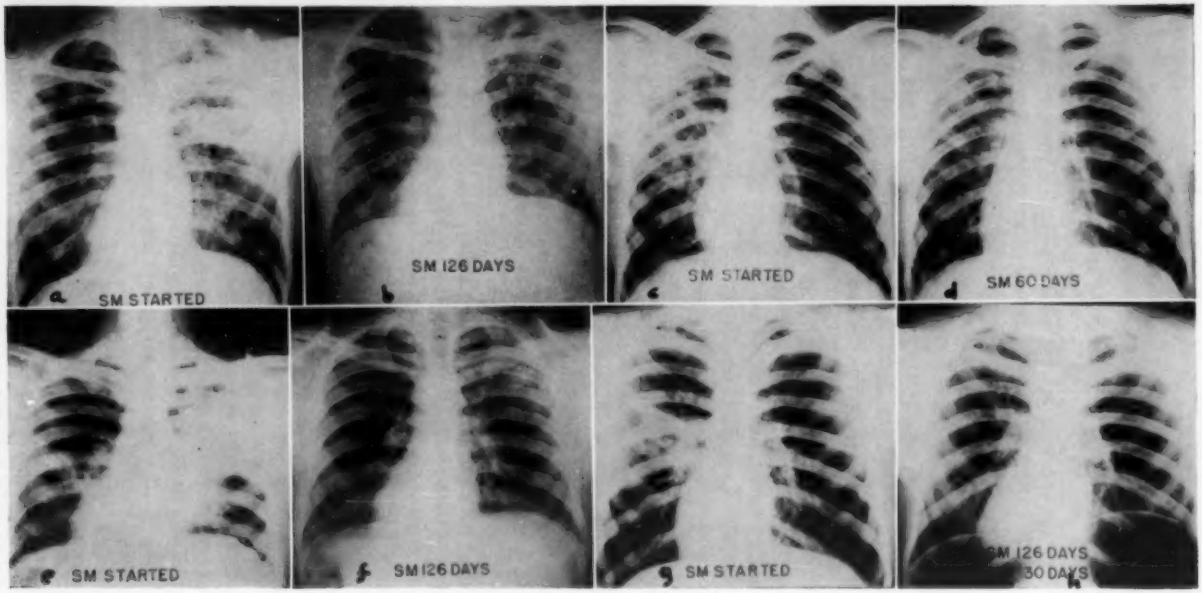

FIG. 1. Classification of roentgenographic regression
(a) and (b) Example of minimal roentgenographic regression
(c) and (d) Example of moderate roentgenographic regression
(e) and (f) Example of excellent roentgenographic regression
(g) and (h) Example of marked roentgenographic regression

Analysis at completion of 126 days of streptomycin therapy revealed that in 2 patients (2.1 per cent) the roentgenographic changes were progressive; in 7 (7.2 per cent) they were stationary; in 23 (23.7 per cent) the changes were classified as minimal regression; in 42 (43.3 per cent), as moderate; in 17 (17.5 per cent), as excellent; and in one (1.03 per cent), as marked regression.

The greatest roentgenographic improvement occurred during the first eighty-four days of therapy. Thereafter, the lesions regressed slowly, remained stationary, or progressed. The first instance of progression occurred between the forty-second and sixty-third days after the start of treatment. The roentgenographic result after 126 days of streptomycin therapy was designated as poor in those patients whose lesions showed minimal regression, no change, or progression.

The most common factor associated with poor roentgenographic response was disease of long duration. Of the 32 patients with poor roentgenographic response at 126 days of streptomycin therapy, 19 (59.4 per cent) had fibrocavernous disease with or without patchy pneumonic areas, 4 (12.6 per cent) had silicotuberculosis, and one (3.1 per cent) had chronic productive disease. Moreover, 21 (65.6 per cent) were 30 years of age or more, and 19 (59.4 per cent) had had known disease for six months or more prior to initiation of therapy. The incidence of the emergence of drug-resistant tubercle bacilli for the entire study and for the 32 patients with poor roentgenographic response was 31.7 and 40.6 per cent, respectively. Of these 32 patients, 27 (84.4 per cent) failed to "convert." This suggests that failure to "convert" and, to a lesser degree, emergence of drug-resistant tubercle bacilli are also important factors which are associated with poor roentgenographic response.

Of the 2 patients whose lesions were progressive, in one definite clinical and roentgenographic progression occurred immediately after the emergence to predominance of drug-resistant bacilli; and in the other, gross hemorrhage followed by spread of disease occurred on the one hundred and ninth day despite the fact that the tubercle bacilli in his sputum were drug-sensitive.

Cavities: Cavitation was graded as small (2 cm. or less), medium (2+ to 4 cm.), and large (4+ or more cm.). A decrease or increase in the cavitary size was designated when the diameter of the cavities changed at least 2 cm. or more during 126 days of therapy. Of the 81 patients with cavity at the initiation of treatment, 37 (45.7 per cent) had large, 37 (45.7 per cent) had medium, and 7 (8.6 per cent) had small cavities. At completion of 126 days of streptomycin therapy, 25 patients (30.8 per cent) had large, 19 (23.5 per cent) had medium, 18 (22.2 per cent) had small cavities, and in 14 (17.3 per cent) the cavities were lost to view. Thoracoplasties had been performed on the remaining 5 (6.2 per cent) patients.

Bacteriologic Status

Streptomycin-resistant Tubercle Bacilli

The first streptomycin-resistant cultures of *M. tuberculosis*, as shown by figure 2, were obtained near the fifty- and eighty-day periods in the far and moderately advanced groups, respectively. No significant difference was noted

in the incidence of drug-resistant bacilli between the one- and two-gram regimens. Following 126 days of streptomycin therapy, the bacteriologic status was unknown in 5 (8.3 per cent) of the patients, 36 (60.0 per cent) were "sensitive," and 19 (31.7 per cent) were "resistant." Of the 19 "resistant" cases, only 3 (15.7 per cent) occurred in the group with moderately advanced tuberculosis.

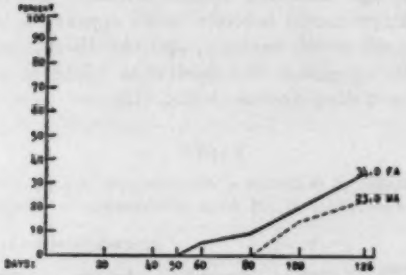

FIG. 2. Incidence of bacterial resistance; far advanced versus moderately advanced groups

Per cent resistant: Total number of patients with known resistant cultures multiplied by 100, divided by total number of patients with positive cultures at the time of evaluation.

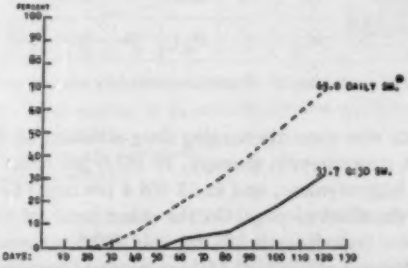

FIG. 3. Incidence of resistance; intermittent versus daily regimens

Per cent resistant: Total number of patients with known resistant cultures multiplied by 100, divided by total number of patients with positive cultures at the time of evaluation.

* See reference 17.

When the rate of the emergence of drug-resistant tubercle bacilli on intermittent streptomycin regimens is compared (figure 3) with that encountered on other daily dosage schedules used at this hospital (17), it is noted that the emergence of bacterial resistance is delayed on intermittent therapy. Since all bacteriologic studies were done in the same laboratory, the influence of technical factors is minimized. This comparison bears out an earlier contention (6) that the development of resistant cases is delayed by intermittent regimens.

An attempt was made to correlate sensitivity studies with cavitary and non-

cavitary disease, far and moderately advanced disease, and old and new disease. Of the 19 patients with drug-resistant tubercle bacilli at 126 days of therapy, 18 (94.7 per cent) were cavitary, 16 (84.2 per cent) had far advanced disease, and 14 (73.7 per cent) had old disease. On the other hand, of the 36 patients with drug-sensitive cultures at 126 days, 29 (80.6 per cent) had cavities, 27 (75.0 per cent) had far advanced disease, and 24 (66.6 per cent) had old disease. Although the percentage differences are not extremely great, the emergence to predominance of drug-resistant tubercle bacilli appears to be most frequently associated with far advanced, cavitary, and old disease (table 2). This is in accordance with the suggestion that cavitation might be a factor associated with the appearance of drug-resistant bacilli (15).

TABLE 2

A Correlation of Cavitation at Initiation of Streptomycin Therapy with Bacteriologic Status at Completion of 126 Days of Streptomycin Therapy

ANALYSIS OF CAVITATION ON INITIATION OF STREPTOMYCIN THERAPY	TOTAL PATIENTS	BACTERIOLOGIC STATUS AT 126 DAYS*							
		Converted		Sensitive		Resistant		Unknown	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Cavernous	81	29	35.1	29	55.8	18	34.6	5	9.6
Noncavernous	16	8	50.0	7	87.5	1	12.5	0	0.0
Totals	97	37	38.1	36	60.0	19	31.7	5	8.3

* Percentages figured according to definitions listed in section on bacteriologic studies

Of the 19 patients who were discharging drug-resistant bacilli prior to completion of 126 days of streptomycin therapy, 10 (52.6 per cent) failed to show any significant clinical improvement, and in 13 (68.4 per cent) the roentgenographic improvement was classified as poor. On the other hand, of the 36 patients with known drug-sensitive organisms at 126 days, 11 (30.5 per cent) had poor clinical result, and 13 (36.1 per cent) showed little or no roentgenographic improvement. This comparison indicates the influence of bacterial sensitivity to streptomycin on streptomycin response; but obviously such factors as increased age and extent and chronicity of disease must be considered as additional causes of the poor therapeutic results observed in these patients.

No patient was definitely known to start discharging drug-resistant bacilli for the first time after streptomycin was discontinued. The shift from relatively sensitive to highly resistant strains of tubercle bacilli usually occurred during a period of ten to fourteen days. The average length of time between the last drug-sensitive and the first drug-resistant culture was eleven days.

Eight patients "converted" for at least ninety days and subsequently discharged tubercle bacilli in the sputum. In every instance the organisms recovered were sensitive to streptomycin *in vitro*. This is in accordance with a previous observation (15).

Reversal of Infectiousness

In the entire group of 97 patients, 37 (38.1 per cent) had "converted" at the 126-day period. An analysis of figure 4 shows that there was a more rapid and greater "conversion rate" in the groups with moderately advanced disease. Little variation was apparent between the MA-1 or MA-2 groups, but a significant difference was noted between the FA-1 and FA-2 series. This variation can probably be attributed to the higher incidence of chronic disease in the FA-1 group.

"Conversion" appears to be a good indication of favorable streptomycin response. Of the 37 patients "converted" at 126 days, only 2 (5.4 per cent) attained a poor clinical result. One of these patients had bronchiectasis and the other had fibrocavernous disease. Of the 37 patients "converted," 4 received

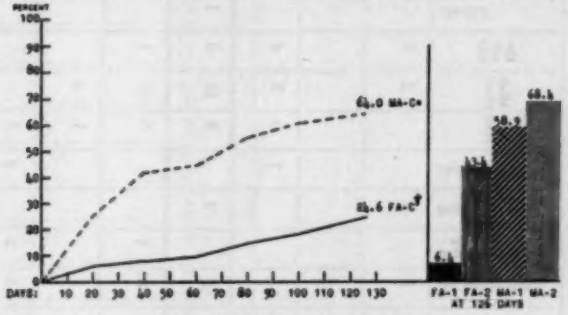

FIG. 4. Percentage of conversion

Per cent converted: Total number of patients converted multiplied by 100, divided by total number of patients analyzed.

* Moderately advanced groups combined.

† Far advanced groups combined.

thoracoplasties prior to completion of 126 days of streptomycin therapy. Of the remaining 33 patients, 17 (51.5 per cent) showed moderate, 10 (30.3 per cent), excellent, and one (3.0 per cent) marked roentgenographic regression, while only 5 (15.2 per cent) showed minimal regression or poor roentgenographic response.

This "conversion rate" of 38.1 per cent, with the favorable clinical and roentgenographic results noted, reflects the therapeutic effectiveness of intermittent streptomycin regimens. The number of "converted" cases had continued to increase at the 189-day evaluation; but because collapse procedures had been freely used after 126 days, no attempt was made to evaluate further streptomycin effect.

Nature of the Lesion

The previous sections have indicated the importance of the nature of the lesion as related to streptomycin response and bacteriologic status. Therefore, analysis by pathologic groupings and their correlation with response to treatment is summarized in table 3.

TABLE 3

Correlation of Pathologic Groupings with the Historical Data, Clinical Status, Roentgenographic Response, and Bacteriologic Status

PRESUMED PATHOLOGY		HISTORICAL				CLINICAL STATUS*			ROENTGENOGRAPHIC RESPONSE AT 126 DAYS†							CAVITY SIZE‡			BACTERIOLOGIC STATUS AT 126 DAYS			
		Extent	Total cases	Age (30 or more)	Onset (6 months or more)	Improvement	No improvement	Improvement with relapse	Progressive	Stationary	Minimal	Moderate	Excellent	Marked	Tcp.	Dec.	Unc.	Inc.	"Converted"	Sensitive	Resistant	Unknown
New disease	Confluent pneumonic	Far Adv.	6	0	0	5	1		1			2	3			2	3		4	1	1	
		Mod. Adv.	0																			
	Patchy pneumonic	Far Adv.	14	4	1	13	1			1	2	7	4			7	2		5	5	3	1
		Mod. Adv.	24	6	10	22	2		1		3	10	9	1		15	2		16	6	1	1
Old disease	Fibrocavernous with patchy pneumonic	Far Adv.	25	12	15	16	6	3			5	17	1		2	8	14	1	3	13	6	3
		Mod. Adv.	6	3	2	5	1				1	4			1	1	4		4	1	1	
	Fibrocavernous	Far Adv.	10	7	7	3	5	2		2	7				1	1	8		1	4	5	
		Mod. Adv.	5	3	4	4	1			1	3				1	1	3		2	2	1	

Chronic productive	Far Adv.	2	2	1	2				1		1							1	1		
	Mod. Adv.	1	0	1	1						1							1			
Silicotuberculosis	Far Adv.	4	4	3	2	1	1		2	2						4			3	1	
	Mod. Adv.	0																			

* No improvement: Sputum more than 30 cc.; fever; cough, moderate or severe; *or* weight loss of ten pounds or more throughout 126-day streptomycin therapy.

Improvement with relapse: Symptoms reduced but with relapse during 126-day streptomycin therapy as defined in *no improvement*.

† Tep. (Thoracoplasties): Thoracoplasties during 126-day streptomycin therapy not evaluated roentgenographically after initiation.

‡ Cavity size: Dec.—decreased; Unc.—unchanged; Inc.—increased.

An attempt was made to describe roentgenograms by common terminology. The six pathologic groupings used in this study and their descriptions are listed below:

(*1*) *Confluent pneumonic:* Consolidated lesion of lobular distribution
(*2*) *Patchy pneumonic:* Disseminated soft lesions giving the "snow-storm" appearance
(*3*) *Fibrocavernous with patchy pneumonic:* Cavitary and fibrous lesions predominating, with an obvious element of "soft" lesions present, usually as a bronchogenic spread
(*4*) *Fibrocavernous:* Cavitary and fibrotic elements outstanding
(*5*) *Chronic productive:* Progressive fibrosing nodular
(*6*) *Silicotuberculosis:* Proved tuberculosis superimposed on silicosis as determined by roentgenographic appearance and occupational history.

Examples of each of the above categories are presented in figure 5. Confluent pneumonic and patchy pneumonic are considered as "new disease," and the remaining four categories are considered as "old disease" in table 3.

Of the 20 patients with *far advanced* and *new disease*, 18 (90.0 per cent) attained a good clinical result, 16 (80.0 per cent) showed favorable roentgenographic changes, and 9 (45.0 per cent) "converted the sputum to negative." Of the 41 patients with *far advanced* and *old disease*, only 23 (56.1 per cent) attained a good clinical result, 19 (46.3 per cent) showed favorable roentgenographic changes, and only 5 (12.2 per cent) "converted their sputum to negative." Of the 24 patients with *moderately advanced* and *new disease*, 22 (91.7 per cent) had good clinical response, 20 (83.3 per cent) showed favorable roentgenographic changes, and 16 (66.6 per cent) "converted their sputum to negative." Of the 12 patients with *moderately advanced* and *old disease*, 10 (83.3 per cent) had good clinical response, 5 (41.7 per cent) attained a good roentgenographic result, and the sputum was "converted to negative" in 7 (58.3 per cent).

Of the 44 patients with *new disease*, 40 (90.8 per cent) had good clinical response, 36 (81.8 per cent) had a good roentgenographic result, and the sputum was "converted to negative" in 25 (56.8 per cent). In contrast, of the 53 patients with *old disease*, only 33 (62.3 per cent) attained a good clinical response, 24 (45.3 per cent) showed favorable roentgenographic changes, and 12 (22.6 per cent) "converted the sputum to negative."

From an analysis of table 4, it is obvious that the changes and degree of improvement under streptomycin therapy are unfavorably influenced by increased chronicity and, to a lesser degree, by the extent of the disease.

Comparison of 126 and 189 Days of Streptomycin Therapy

To determine the advantages of postponing the emergence of drug-resistant bacilli and hence prolonging the total period of streptomycin activity, a comparison of the efficacy of four and six months of streptomycin therapy was attempted. Since we were evaluating, as nearly as possible, only the streptomycin effect obtained, no patients who developed bacterial resistance or received collapse therapy prior to 189 days were included.

At 126 and 189 days, a comparison was made between the bacteriologic status, clinical response, and roentgenographic response of patients who received four

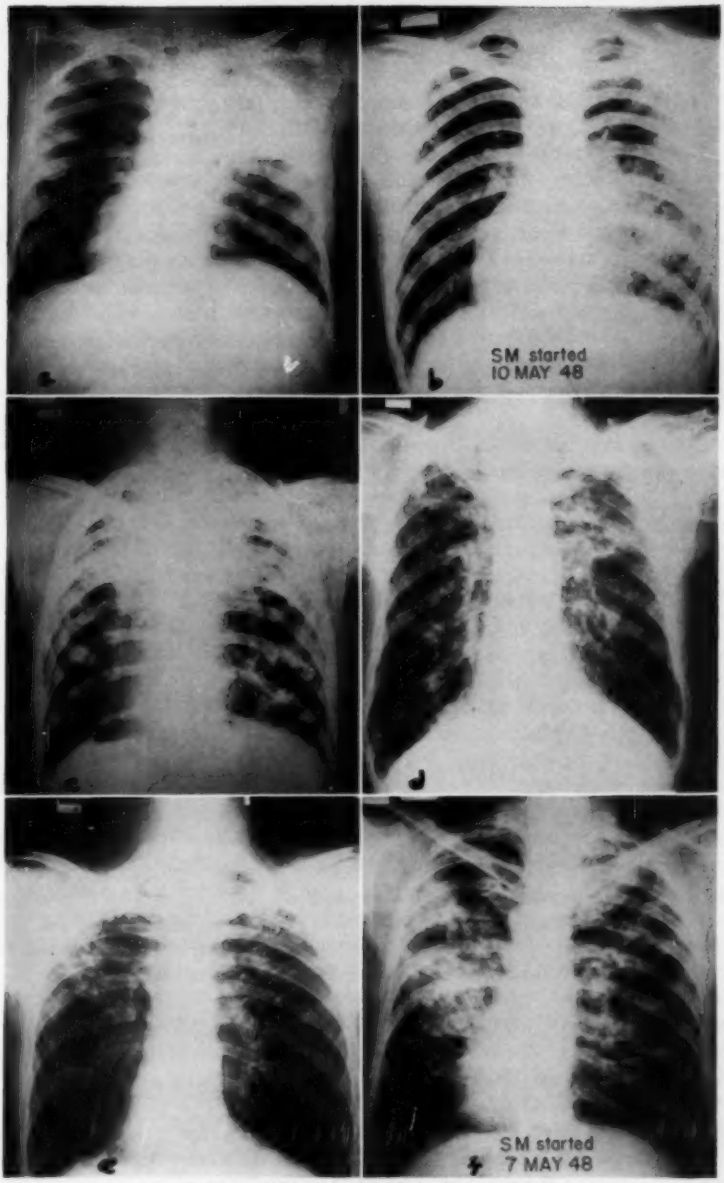

FIG. 5. Exemplification of pathologic classification

(a) Confluent pneumonic disease
(b) Patchy pneumonic disease
(c) Fibrocavernous with patchy pneumonic disease
(d) Fibrocavernous disease
(e) Chronic productive disease
(f) Silicotuberculosis

and six months of intermittent streptomycin therapy, respectively. No appreciable change was noted in the clinical and roentgenographic response or in the number of sputum "conversions." Analysis of the age, onset, extent, and presumed pathology of the disease in each patient, however, results in groups statistically insignificant. Consequently, no definite conclusions concerning the benefits obtained from prolonging sensitivity and resultant effective streptomycin therapy beyond 126 days can be derived from this analysis.

The desirability and advantages of prolonging effective streptomycin preparation and protection for necessary temporary and permanent surgical procedures are generally recognized. Thoracoplasties were successfully performed on an average of 129 days following initiation of therapy on 10 patients. A course of intermittent streptomycin therapy was of an average of 175 days' duration in

TABLE 4

Relation of Type of Lesion to Therapeutic Result

EXTENT AND TYPE OF DISEASE	NUMBER OF PATIENTS	GOOD CLINICAL RESULT	GOOD ROENTGENOGRAPHIC RESULT	SPUTUM CONVERSION
Far advanced and new disease	20	18 (90.0 per cent)	16 (80.0 per cent)	9 (45.0 per cent)
Far advanced and old disease	41	23 (56.1 per cent)	19 (46.3 per cent)	5 (12.2 per cent)
Moderately advanced and new disease	24	22 (91.7 per cent)	20 (83.3 per cent)	16 (66.6 per cent)
Moderately advanced and old disease	12	10 (83.3 per cent)	5 (41.7 per cent)	7 (58.3 per cent)
New disease	44	40 (90.8 per cent)	36 (81.8 per cent)	25 (56.8 per cent)
Old disease	53	33 (62.3 per cent)	24 (45.3 per cent)	12 (22.6 per cent)

each instance. No complications or spreads of disease were encountered and, at completion of the study, sputum "conversions" had occurred in 6 (60.0 per cent) patients. Streptomycin sensitivity studies on tubercle bacilli obtained from the remaining 4 patients revealed drug-sensitive organisms in each instance.

Comment and General Summary

To determine the efficacy of intermittent streptomycin regimens, 97 patients with pulmonary tuberculosis were treated with 1 or 2 gm. of streptomycin every third day for 126 to 189 days.

All were males, and 43 (44.3 per cent) were 30 years or more of age. Of the 97 patients, 61 (62.8 per cent) had far advanced disease, 81 (83.5 per cent) exhibited evidence of cavitation, and 53 (54.6 per cent) had old disease.

Clinical evaluation, based on analysis of fever, sputum quantity, cough, body weight, and erythrocyte sedimentation rate, showed that improvement occurred in 73 (75.3 per cent) of the patients at completion of 126 days of ther-

apy. Fever, sputum quantity, and cough usually improved most rapidly during the first 42 days of treatment. Of the 40 patients with febrile tuberculosis at initiation of therapy, 67.5 and 90.0 per cent were afebrile after 21 and 126 days of treatment, respectively. The most common factors associated with poor clinical response were increased extent and chronicity of disease and, to a lesser degree, the development of bacterial resistance.

The incidence of streptomycin toxicity was 1.03 per cent and 5.0 per cent at completion of 126- and 189-day courses of intermittent streptomycin therapy, respectively. The toxicity encountered in each patient was mild, transient, and did not necessitate the discontinuation of streptomycin.

Of the 13 patients with endobronchial tuberculosis, all but one showed complete recession of their lesions in less than 126 days. In most cases, complete recession occurred within 42 days of treatment.

The greatest roentgenographic changes occurred during the first 84 days of therapy. After 126 days, 60 (61.8 per cent) of the patients showed moderate, excellent, or marked roentgenographic changes of a favorable nature.

At 126 days, bacteriologic "conversions" of at least three months' duration had occurred in 37 (38.1 per cent) of the patients treated with intermittent regimens. This compares favorably with a "conversion rate" of 19 per cent attained on previous daily dosage schedules of similar duration. At the 126-day point, conversion of sputum had occurred in 64.0 and 24.6 per cent of the moderately and far advanced cases, respectively. The number of "conversions" continued to increase up to 189 days after the start of treatment.

At completion of 126 days of therapy, the drug-sensitivity of the tubercle bacilli was unknown in 5 patients (8.3 per cent); 36 (60.0 per cent) patients yielded sensitive organisms; and 19 (31.7 per cent) patients yielded drug-resistant organisms. At this time (126 days) the incidence of drug-resistant bacilli in the moderately advanced groups was 23.0 and 34.0 per cent, respectively. At completion of 126 days of therapy, the incidence of patients with drug-resistant tubercle bacilli in the present study was only 31.7 per cent as compared with an incidence of 69.0 per cent encountered at this hospital with previous daily dosage schedules of similar duration. When the phenomenon of drug resistance appeared, the shift from relatively sensitive to highly resistant strains of tubercle bacilli usually occurred during a period of ten to fourteen days. Eight patients "converted to negative" for ninety days or more but subsequently discharged tubercle bacilli in the sputum. The organisms recovered were sensitive to streptomycin in every instance. Of the 81 patients with cavities, 18 (34.6 per cent) of the 52 who continued to discharge tubercle bacilli were discharging drug-resistant organisms at 126 days. In contrast, of the 16 patients without cavities, only one (12.5 per cent) of the 8 who remained "positive" was discharging drug-resistant bacilli.

Thoracoplasties were successfully performed on 10 patients at an average of 129 days following initiation of streptomycin therapy. No complications or spreads of disease were encountered. At completion of the study, sputum "conversions" had been accomplished in 6 of these patients and streptomycin sens-

itivity studies on bacilli from the remaining 4 patients revealed drug-sensitive organisms in each instance.

The relative efficacy of the one- and two-gram schedules could not be determined.

The decreased incidence of streptomycin toxicity, the delay in the emergence of bacterial resistance, and the therapeutic efficacy of intermittent streptomycin regimens emphasize the importance of determining the results of combining para-aminosalicylic acid and other antituberculous agents with intermittent dosage schedules(6).

SUMMARY

1. In a study of the intermittent administration of streptomycin (1 or 2 gm. every third day), the clinical and roentgenographic results were comparable to those obtained with previous daily dosage schedules.

2. Intermittent administration of streptomycin results in a marked reduction in the incidence of toxic reactions to the drug.

3. The use of intermittent regimens delays the emergence of streptomycin-resistant strains of *M. tuberculosis*.

4. The "conversion rate" by the intermittent administration of streptomycin in the present study was appreciably greater than that observed on previously used daily dosage schedules of similar duration.

5. The efficacy of streptomycin in the treatment of pulmonary tuberculosis diminishes as the chronicity and, to a lesser degree, extent of the disease increase.

SUMARIO

Regímenes Intermitentes de Estreptomicina. Análisis de 97 Enfermos con Tuberculosis Pulmonar, Tratados con Uno o Dos Gramos de Estreptomicina Cada Tres Días

1. En el estudio actual, las respuestas clínica y roentgenológica fueron comparables con las obtenidas con previos esquemas de dosis diaria.

2. La administración intermitente de estreptomicina logra una notable disminución en la incidencia de reacciones tóxicas a la droga.

3. El empleo de regímenes intermitentes retarda la aparición de cepas estreptomicinorresistentes del *M. tuberculosis*.

4. El índice de viraje del esputo obtenido con la administración intermitente de estreptomicina es apreciablemente mayor que el conseguido con previos esquemas de dosis diaria, de duración semejante.

5. La eficacia de la estreptomicina en el tratamiento de la tuberculosis pulmonar disminuye a medida que aumentan la cronicidad y, en menor grado, la difusión de la enfermedad.

RESUME

Administration intermittente de stretpomycine. Analyse des observations de 97 malades atteints de tuberculose pulmonaire et traités avec un ou deux grammes de streptomycine tous les trois jours

1. Dans cette étude, les résultats cliniques et radiologiques sont comparables à ceux obtenus avec le programme de dosage journalier antérieur.

2. L'administration intermittente de la streptomycine a déterminé une réduction notable de l'incidence des réactions de toxicité de la drogue.

3. L'administration discontinue retarde l'apparition de souches résistantes de *M. tuberculosis*.

4. Dans cette étude le taux de conversion par l'administration intermittente de streptomycine est nettement plus élevé que celui obtenu avec le dosage quotidien antérieur de même durée.

5. L'efficacité de la streptomycine dans le traitement de la tuberculose pulmonaire diminue au fur et à mesure que la chronicité et, à un moindre degré, l'étendue de la maladie s'accroissent.

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COMBINED INTERMITTENT REGIMENS EMPLOYING STREPTOMYCIN AND PARA-AMINOSALICYLIC ACID IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

A Comparison with Daily and Intermittent Dosage Schedules

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INTRODUCTION

Previous laboratory and clinical investigations have proved that both streptomycin (SM) and para-aminosalicylic acid (PAS) are active against the tubercle bacillus *in vitro*, and favorably affect the trend of tuberculosis in humans. A major objective of recent clinical studies has been to determine the most satisfactory regimen of these two drugs in terms of therapeutic effectiveness, prolongation of bacterial sensitivity, and reduction of drug toxicity.

An abundance and variety of clinical material has permitted the study of relatively large series of patients on various dosage schedules in the United States Army Tuberculosis Center at Fitzsimons Army Hospital, Denver, Colorado. The principal regimens investigated are listed in table 1. The first study, employing streptomycin 1.8 to 2 gm. in divided doses daily for 120 days, was started in April 1946. This program produced a high incidence of drug-resistant organisms and damage to the vestibular and auditory apparatus. The succeeding regimens (table 1, regimen numbers 2, 3, 4, and 5) investigated during the ensuing two and one-half years were characterized by successive reduction in daily dose and duration of treatment. Drug toxicity was partially decreased by the smaller doses, and the incidence of bacterial resistance was decreased by shorter duration of therapy. However, small doses of streptomycin for short periods (table 1, regimen numbers 4 and 5), though desirable from the standpoint of low incidence of toxicity and bacterial resistance, were impracticable because they were therapeutically inadequate in many types of pulmonary tuberculosis. By the repetition of short courses (table 1, regimen number 7) therapeutic effectiveness was again obtained, but there was a corresponding increase in the incidence of bacterial resistance (1). Previous investigators have shown that: (a) tubercle bacilli reproduce in the test tube approximately every one and one-half to three and one-half days (2); (b) streptomycin is most active against multiplying tubercle bacilli (3); and (c) streptomycin is capable of exerting sustained therapeutic activity in guinea pigs when administered intermittently (4). These observations suggested that the intermittent administration

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[2] Presented before the Medical Session, as part of the symposium on *Chemotherapy*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 25, 1950

of streptomycin might be therapeutically satisfactory. As a consequence, two regimens (table 1, regimens 8 and 9) based on this concept were investigated and became the treatments of choice during 1948 and early 1949 (5). The incidence of toxicity was low and clinical effectiveness was preserved, but the problem of bacterial resistance was not solved.

TABLE 1

Incidence of Drug-resistant Strains of M. Tuberculosis on Eleven Experimental Regimens

REGIMEN NUMBER	DRUG	DOSAGE SCHEDULE	NUMBER OF PATIENTS (TOTAL 568)	PERCENTAGE RESISTANT*
Daily Dosage Regimens				
1	SM	2 GM Q D for 120 D	100	74
2	SM	1 GM Q D for 120 D	37	68
3	SM	1 GM Q D for 42 D	21	25
4	SM	1 GM Q D for 28 D	67	5
5	SM	0.5 GM Q D for 28 D	28	0
6	PAS	12 GM Q D for 120 D	50	53
Interrupted Short-Course Regimen				
7	SM	1 GM Q D for 28 D, repeated after 42 D	35	30
Intermittent Dosage Regimens				
8	SM	1 GM Q 3 D for 120 D	50	34
9	SM	2 GM Q 3 D for 120 D	50	32
10	DHSM	2 GM Q 3 D for 30 D	20	0
Combined Intermittent Dosage Regimen				
11	SM PAS	1 or 2 GM Q 3 D 12 GM Q D } for 120 D	102	0

* Calculated from the number of patients with cultures resistant to streptomycin or PAS on or after 120 days of therapy, divided by the number of patients on whom positive cultures were obtained on or after 120 days of therapy, expressed as a percentage of the latter. Resistance is defined as growth on medium containing 10 γ per ml. of either drug comparable to growth on control (0 γ per ml.)

In February 1949, clinical trial of the daily administration of para-aminosalicylic acid was started (table 1, regimen number 6). Clinical appraisal of the results is given in detail in this paper.

Demerec (6) postulated that, "... the most effective way theoretically of preventing the origin of resistant strains of bacteria ... is the use in clinical treatment of a mixture of two antibiotics ... that affect the same pathogen but are independent in their actions." Karlson and co-workers (7) observed in 5 patients who received streptomycin and para-aminosalicylic acid for 90 days that bacterial resistance to streptomycin occurred in only the one patient whose

bacilli had not been tested for drug sensitivity at the start of treatment. Accordingly, in May 1949 an investigation was started at Fitzsimons of the effectiveness of a combined intermittent regimen in which both streptomycin and PAS were used. The regimen consisted of the intramuscular administration of streptomycin, 1 or 2 gm. every third day, and the oral administration of 12 gm. of para-aminosalicylic acid daily. The total period of drug therapy was 120 days (table 1, regimen 11) (8).

REGIMENS STUDIED AND METHOD OF EVALUATION

In the present report four regimens (table 2) are compared in each of which the duration of treatment was 120 days. The regimens are: streptomycin administered daily; para-aminosalicylic acid administered daily; streptomycin

TABLE 2

Patients Studied, Classified by Regimen

REGIMEN		NUMBER OF PATIENTS
I	DAILY STREPTOMYCIN	
	SM, 1 or 2 gm. intramuscularly daily for 120 days	66
II	DAILY PARA-AMINOSALICYLIC ACID	
	PAS, 12 gm. orally daily for 120 days	25
III	INTERMITTENT STREPTOMCYIN	
	SM, 1 or 2 gm. intramuscularly every third day for 120 days	97
IV	INTERMITTENT SM COMBINED WITH DAILY PAS	
	SM, 1 or 2 gm. intramuscularly every third day; PAS, 12 gm. orally daily; total duration of chemotherapy, 120 days	95

administered every third day; and, derived from the two preceding, streptomycin administered every third day combined with para-aminosalicylic acid administered daily (table 2).

The daily streptomycin regimen is subsequently referred to as SM DAILY, the daily para-aminosalicylic acid regimen as PAS DAILY, the intermittent streptomycin as SM Q 3 DAY, and combined intermittent (streptomycin every third day, para-aminosalicylic acid daily) regimen as SM-PAS. Evaluations were made on the basis of clinical, roentgenographic, and bacteriologic responses and drug toxicity.

Clinical criteria were: (a) alterations of temperature, (b) variations of weight in excess of five pounds, and (c) changes of sputum volume in excess of 15 cc. Patients were considered improved if there was a favorable change in any one of these clinical factors without worsening in the remainder.

Roentgenograms of the chest were evaluated by a jury of no less than three of the writers in terms of trend of the pulmonary lesion and presence of cavity. Trend was defined as marked improvement, moderate improvement, slight improvement, no change, or worsening. *Marked improvement* referred to complete or almost complete resolution. Minimal but

unequivocal degrees of resolution were graded as *slight improvement*. *Worsening* was defined as any degree of extension of the disease in any part of the roentgenogram, even if other areas were improved. *Presence of cavity* was recorded if the outline could be clearly seen.

Bacteriologic evaluation of sputum was made by accepted smear and culture techniques and of fasting gastric contents by culture alone (9). "Conversion" of sputum was defined according to National Tuberculosis Association standards, i.e., bacteriologically negative for three consecutive months. The bacteriologic status of patients whose sputum or gastric studies were negative for a period of less than three months at the evaluation date was called "indeterminate."

Sensitivity studies to both drugs, when appropriate, were performed at approximately weekly intervals on Herrold's egg-yolk agar (10). After ten to fourteen days of incubation, growth on medium containing the drug was evaluated by comparison with the control. Cultures showing growth on the 10 γ per ml. tube equal to that on the control (0 γ per ml.) were arbitrarily called resistant (11).

The incidence and severity of toxic manifestations were determined by appropriate clinical and laboratory studies, with particular attention to detection of damage to the auditory apparatus, hepatic and renal insufficiency, blood dyscrasias, dermatitis, and gastrointestinal disturbances.

Evaluation of clinical, roentgenographic, and bacteriologic data was made at the following periods: (a) at the date of commencement of drug treatment for the 60 days immediately preceding therapy to establish the trend at the zero day; (b) at the time of completion of therapy (120 days) in relation to the zero-day point; (c) at 180 days from the beginning of therapy (60-day post-treatment evaluation) in relation to the 120-day point.

ANALYSIS OF CLINICAL MATERIAL

The following requirements determined which patients were studied on the four regimens: (a) moderately or far advanced nonmiliary pulmonary tuberculosis with tubercle bacilli demonstrated at beginning of therapy, (b) no previous streptomycin or para-aminosalicylic acid treatment, and (c) deferment of operative procedures until completion of 120 days of drug therapy.

The average age of the patients ranged from 25 to 33 years. In each series, sex and race were predominantly male and white, respectively. Sixty-three per cent of the cases in the SM DAILY and SM Q 3 DAY groups had far advanced disease, and 44 per cent of the PAS DAILY and SM-PAS groups were in this category. The known duration of the disease was less than six months in 53 to 68 per cent and more than eighteen months in 4 to 16.6 per cent of the patients in the various groups.

Each case was given a clinical pathological classification based primarily on a comparison of serial roentgenograms, with consideration of duration of disease and clinical course (12). As shown graphically (figure 1), the pattern representing the percentage of cases in each clinical pathological group was similar for the four regimens.

The incidence of cavitation at the day of onset of treatment was approximately equal for each of the series studied, namely, 94 per cent for SM DAILY, 92 per cent for PAS DAILY, 90 per cent for SM Q 3 DAY, and 87.5 per cent for SM-PAS.

The trend of disease at the zero-day point (determined by comparison of the zero-day roentgenogram with films taken within the preceding 60 days) revealed similar distribution patterns for each of the four treatment schedules (figure 2).

The incidence of tuberculous complications at the zero-day point was 27.3 per cent for SM DAILY, 8 per cent for PAS DAILY, 18.6 per cent for SM Q 3 DAY, and 17.8 per cent for combined SM-PAS. Complications, which included endobronchial and laryngeal tuberculosis (proved by endoscopic examination),

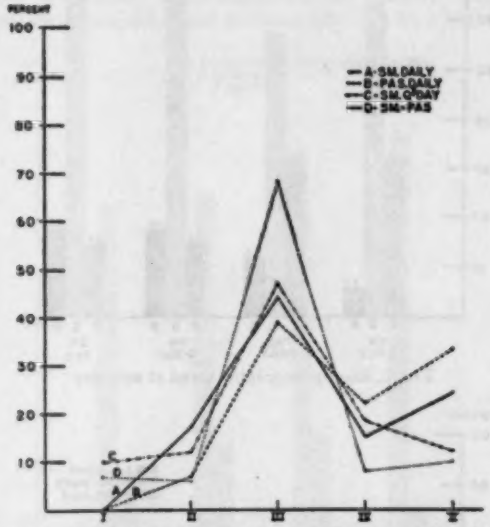

FIG. 1. Percentage distribution of patients according to pathologic groups. Clinical pathological classification, based chiefly on serial roentgenograms:

I. New, resolving lesions (exudative)
II. New, poorly resolving lesions (caseous pneumonic)
III. New, mixed lesions (exudative, caseous pneumonic)
IV. Old, irreversible lesions (fibrocaseous)
V. Mixed new and old lesions

hemoptysis, pleural effusion, and gastrointestinal and other types of extrapulmonary tuberculosis, were recorded when they existed or developed at any time during the course of treatment or during the 60-day post-treatment period. No instances of miliary tuberculosis or tuberculous meningitis were encountered.

EVALUATION AFTER ONE HUNDRED AND TWENTY DAYS OF THERAPY

Clinical status: The clinical status, i.e., improved, worsened, or unchanged, after 120 days of therapy compared with the status at the zero-day point is shown in figure 3. Improvement ranged from 56 per cent of the patients on PAS DAILY to 72.8 per cent of those on SM DAILY. Worsening varied from 8 per

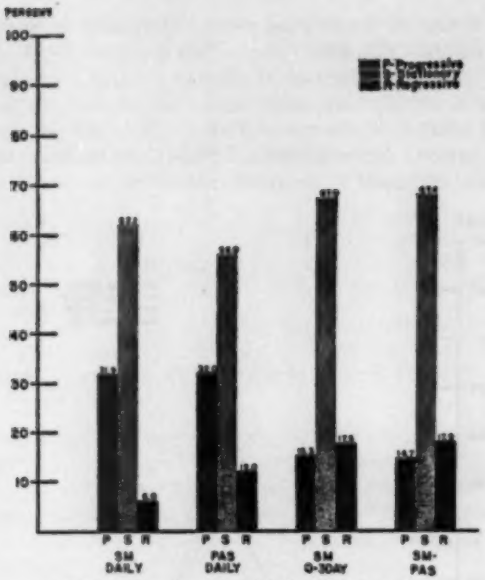

FIG. 2. Roentgenographic trend at zero day

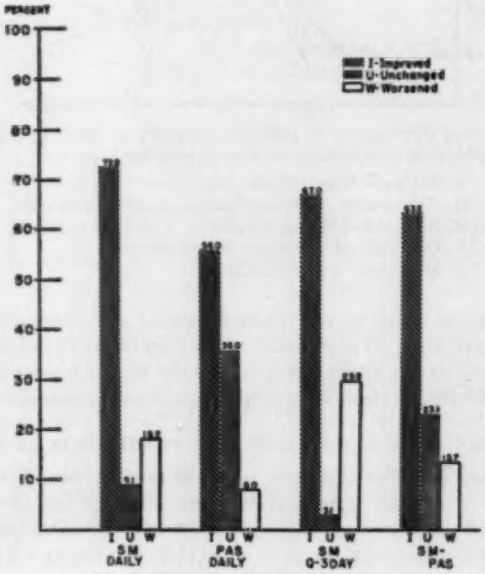

FIG. 3. Clinical evaluation at 120 days

cent of the 25 patients who received PAS DAILY to 29.8 per cent of those who were given SM Q 3 DAY.

Roentgenographic evaluation: Comparison of the 120-day roentgenogram with that taken at the zero-day point established the roentgenographic trend, i.e., slight, moderate, or marked degrees of improvement, no change, or worsening. The patients who received SM-PAS showed the highest proportion of improvement (figure 4), particularly in the "moderate" and "marked" categories with fewer patients "unchanged" or "worsened." The patients who received SM DAILY showed improvement equal to those who received SM Q 3 DAY. The

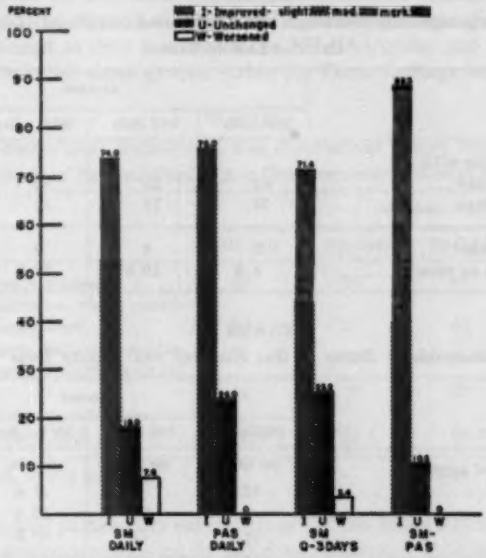

FIG. 4. Roentgenographic evaluation at 120 days

PAS DAILY patients showed approximately the same total improvement as the SM DAILY and the SM Q 3 DAY patients, but in the majority improvement was only "slight."

Of the patients in each regimen with roentgenographic evidence of cavitation at the zero-day point, not more than 20.5 per cent showed cavity lost to view after 120 days of therapy (table 3). The best results were obtained with the SM-PAS treatment program.

Bacteriologic evaluation: sputum "conversion": "Sputum conversions," according to National Tuberculosis Association standards and based on the number of patients in each series, were: SM DAILY, 15 per cent; PAS DAILY, 8 per cent; SM Q 3 DAY, 21.6 per cent; and SM-PAS, 37 per cent (table 4). The percentages of patients with persistently "positive" sputum varied from 33.8 per cent in the SM-PAS series to 76 per cent in the SM DAILY group. The incidence of

patients with "indeterminate" sputum, i.e., bacteriologically negative for less than 90 days, was greatest in the SM-PAS series, which suggests a trend toward ultimate "conversion" in many of these individuals. It is interesting to note that approximately 50 per cent of the patients on the four regimens studied whose sputum had "converted" during therapy showed persistence of cavity on the 120-day roentgenograms.

Bacteriologic evaluation: emergence of resistant organisms: Cultures of *M. tuberculosis* obtained from all patients were sensitive to streptomycin and para-

TABLE 3

Roentgenographic Evaluation at One Hundred and Twenty Days

Cavities Lost to View

	REGIMEN			
	SM Daily	PAS Daily	SM Q 3 Day	SM-PAS
Number of patients with:				
Cavity at zero day	62	23	82	83
Cavity at 120 days	59	19	73	66
Cavity lost to view	3	4	9	17
Percentage lost to view	4.8	10.9	17.4	20.5

TABLE 4

Bacteriologic Status at One Hundred and Twenty Days

	REGIMEN			
	SM Daily	PAS Daily	SM Q 3 Day	SM-PAS
Bacillary status of sputum:	*per cent*	*per cent*	*per cent*	*per cent*
Converted*	15	8	21.6	37.0
Indeterminate†	9	20	15.5	29.6
Positive	76	72	63.0	33.8

* According to National Tuberculosis Association standards, at 120 days.

† Negative, but for less than 90 days at the 120-day evaluation point.

aminosalicylic acid at the beginning of treatment. Drug resistance is calculated as the number of patients with cultures resistant to either drug on or after 120 days of therapy divided by the number of patients on whom positive cultures were obtained on or after 120 days of therapy, expressed as a percentage of the latter.

The high incidence of bacteriologically negative cases in the SM-PAS group at the 120-day evaluation point reduces the number of cultures for resistance studies. Analysis of the current data on this regimen shows that resistance studies have been performed on cultures from 95 patients at the beginning of therapy, 65 after 30 days' treatment, 47 after 60 days, 30 after 90 days, and 26 after 120 days of therapy. Follow-up studies also have been completed on cultures from

16 patients at 30 days and 10 patients at 60 days following therapy. No instance of loss of *in vitro* bacterial sensitivity to either drug has been encountered to date (table 5).

Only in the regimen employing two drugs, i.e., streptomycin and para-aminosalicylic acid, have no resistant organisms been encountered to date.

As mentioned previously, the series of patients studied on the four regimens showed similar pathologic grouping and incidence of cavity at the zero-day point. Of the patients who continued to discharge tubercle bacilli after 120 days of drug treatment, 87 per cent of those on the SM-PAS regimen and 83 to 94 per cent of those on the other three regimens showed roentgenographic persistence of cavity at the end of treatment. Nevertheless, loss of bacterial sensitivity has occurred to date in none of the SM-PAS group and in 33.3 to 75.9 per cent of the other three groups (table 5). These findings indicate that the

TABLE 5

Bacteriologic Evaluation at One Hundred and Twenty Days

Incidence of Patients Discharging Drug-resistant* Tubercle Bacilli

	REGIMEN			
	SM Daily	PAS Daily	SM Q 3 Day	SM-PAS
Number of patients studied	66	25	97	95
Number of patients on whom resistance studies completed	54	18	66	28
Number of patients discharging drug-resistant* tubercle bacilli on or after 120 days	41	6	22	0
Percentage of patients with drug-resistant* tubercle bacilli	75.9	33.3	33.3	0.0

* To SM, PAS, or SM and PAS.

type of disease, and particularly cavitation, are of less importance in determining emergence of resistant strains up to 120 days of therapy than is the treatment employed. This is contrary both to the writers' observations prior to the employment of combinations of drugs and to the published experiences of others using streptomycin alone (13).

The rate of emergence of resistant organisms is best shown by the work of one of the writers (11) studying this phenomenon in a larger series of cases in which those reported in this paper are included (figure 5). From this line graph it may be seen that SM DAILY dosage regimens resulted in the emergence of drug-resistant bacilli as early as the thirtieth day of treatment, while with SM Q 3 DAY administration the rate of emergence as well as the total incidence were significantly lower. In 50 patients treated with PAS DAILY, emergence of drug-resistant tubercle bacilli was delayed to the sixtieth day, while in those patients treated with combined intermittent therapy no loss of bacterial drug sensitivity has yet been encountered after 120 days of treatment.

The emphasis on short courses of streptomycin or para-aminosalicylic acid is

related to the rate of emergence of resistant organisms and to the duration of therapeutic effect, as has been described by two of the writers (14). Since drug resistance has not yet been demonstrated when the two drugs are used as described here, the fear of loss of sensitivity need not limit treatment to less than 120 days if longer courses seem desirable.

Toxicity: The incidence of toxicity encountered on the four regimens studied is shown in figure 6. The patients treated with streptomycin, 1 or 2 gm. daily for 120 days, showed a far greater incidence (57.5 per cent) of toxic reactions than those treated on any of the other regimens. Moreover, even this incidence of 57.5 per cent toxic reactions is lower than that reported in larger series of cases (15). It is interesting that the incidence of drug reaction encountered with

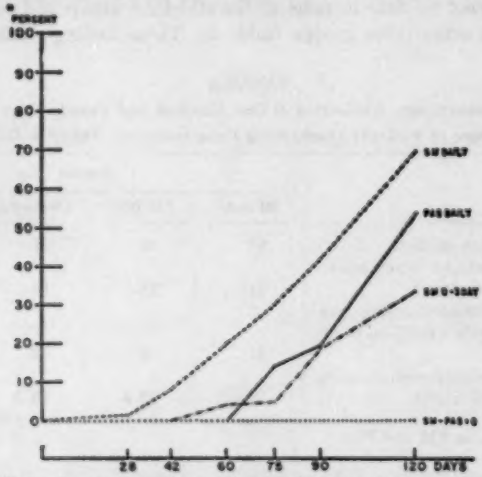

FIG. 5. Rate of emergence of organisms resistant to streptomycin and PAS
* Percentage of patients with cultures positive for tubercle bacilli at time of evaluation

combined intermittent SM-PAS is slightly higher than that encountered when each of the components was administered separately. In 4 of the 13 patients who showed toxic reactions to the intermittent combined SM-PAS treatment, the reactions were of sufficient severity to require cessation of therapy (2 dermatitis, one dermatitis with coincident hepatitis, and one severe gastrointestinal distress). All 4 patients recovered promptly from the evidences of drug intolerance when therapy was stopped. Minor reactions encountered on the combined intermittent regimen consisted of transient epigastric distress and diarrhea, mild skin eruptions, and impaired response to caloric stimulation without subjective vertigo.

EVALUATION AT SIXTY DAYS POST TREATMENT

Evaluation made 60 days following the 120-day courses of therapy was limited to consideration of clinical, roentgenographic, and bacteriologic relapse,

because in this period it was necessary in many instances to supplement the prior therapy with re-treatment (drug therapy) or operative procedures (tables

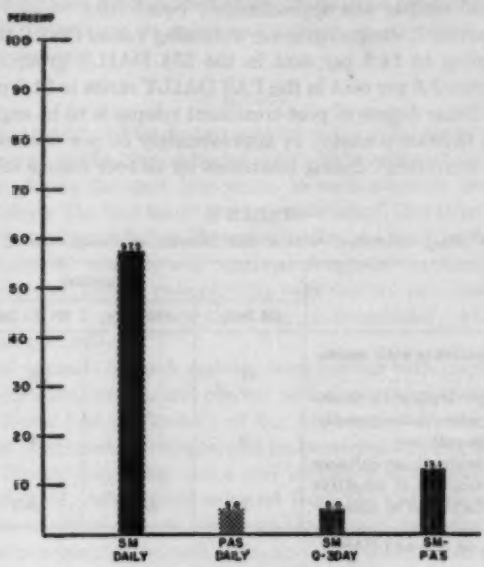

FIG. 6. Incidence of toxicity

TABLE 6

Evaluation at Sixty Days Post Treatment

	REGIMEN			
	SM Daily	PAS Daily	SM Q 3 Day	SM-PAS
Number of patients observed.....	27	17	91	33
	per cent	*per cent*	*per cent*	*per cent*
Clinical relapse*.....	22.2	17.6	16.5	15.1
Roentgenographic worsening†.....	14.8	0	5.9	9.0
Sputum reversions‡.....	12.5	5.5	9.1	31.2

* Worsening in any single clinical criterion.

† Worsening between 120 and 180 days.

‡ "Converted" (NTA standards) at 120 days but again "positive" at 180 days.

6 and 8). Clinical relapse was defined as worsening in any of the factors previously analyzed. Roentgenographic relapse was recognized if progression of disease was demonstrated in a roentgenogram taken 60 days post treatment, in comparison with one taken at the completion of the course of drug treatment. Bacteriologic relapse refers to those patients whose sputum converted at 120 days, but again became positive for tubercle bacilli during the ensuing 60 days.

The percentages of relapse are based on the number of patients observed at the 60-day post-treatment point upon whom complete studies were available (table 6). Clinical relapse was approximately equal (15.1 to 22.2 per cent) on each of the regimens. Roentgenographic worsening varied from 0 per cent in the PAS DAILY group to 14.8 per cent in the SM DAILY group. Bacteriologic relapse ranged from 5.5 per cent in the PAS DAILY series to 31.2 per cent in the SM-PAS series. Some degree of post-treatment relapse is to be expected in view of the fact that cavities persisted in approximately 50 per cent of the patients whose sputum "converted" during treatment on all four dosage schedules.

TABLE 7

Disappearance of Drug-resistance within Six Months of Completion of Drug Therapy*

	REGIMEN			
	SM Daily	PAS Daily	SM Q 3 Day	SM-PAS
Total number of patients with resistant cultures	41	6	22	0
Total number of patients with resistant cultures who subsequently yielded sensitive cultures	0	5	4	—
Percentage of patients whose cultures reverted from resistant to sensitive within six months of end of therapy	0	83.3	18.1	—

* To SM, PAS, or SM and PAS.

TABLE 8

Operative Procedures Performed Following Chemotherapy*

	REGIMEN			
	SM Daily	PAS Daily	SM Q 3 Day	SM-PAS
Percentage of patients receiving operative procedures	36.4	60	75.2	50

* Temporary or permanent collapse or excisional surgery.

The incidence of patients whose cultures were resistant at the end of therapy and who during a six-month period of subsequent observation yielded drug-sensitive cultures is shown in table 7. The fact that this phenomenon is especially marked with only one regimen, PAS DAILY, minimizes the likelihood of cross-contamination or superinfection as a causative factor. The magnitude of the loss of drug resistance may approach 100 per cent during a longer post-treatment observation period, and presumably will be accompanied by restoration of the therapeutic effectiveness of para-aminosalicylic acid.

The percentages of patients in each series who received temporary or permanent collapse procedures or excisional surgery after the 120-day point are shown in table 8. These percentages varied from 36.4 per cent in the SM DAILY series

to 75.2 per cent in the intermittent streptomycin series. The figures are illustrative of the writers' belief that drug therapy is rarely definitive for nonmiliary pulmonary tuberculosis, but enables more patients to have the advantages of various collapse procedures or excisional surgery at an earlier date with less danger of complications

SUMMARY

A comparative study of four dosage schedules in a total series of 283 patients has been conducted at the United States Army Tuberculosis Center, Fitzsimons Army Hospital, during the past four years. In each schedule the patients were treated for 120 days. The four study groups consisted of: 66 patients who received streptomycin, 1 or 2 gm. daily; 25 patients who received para-aminosalicylic acid, 12 gm. daily; 97 patients who received streptomycin intermittently, 1 or 2 gm. every third day; and 95 patients who were treated on a combined regimen of streptomycin, 1 or 2 gm. every third day, concomitantly with para-aminosalicylic acid, 12 gm. daily.

The groups of patients on each regimen were similar with respect to age, sex, and race. The duration, extent, and clinical pathologic types of disease were also similar. All patients had moderately or far advanced pulmonary tuberculosis bacteriologically confirmed by culture, and had received no prior antituberculous drug therapy. Roentgenographic trend and incidence of cavitation were alike, and the strains of *M. tuberculosis* cultured from the patients were uniformly sensitive *in vitro* to either or both agents at the time of initiation of treatment.

Clinical, roentgenographic, bacteriologic, and drug toxicity factors were evaluated after 120 days of treatment. Analysis of these data showed that:

(a) Clinical response, in terms of reduction of fever, reduction of sputum volume, and weight gain, was equivalent on all four regimens.

(b) The combined intermittent regimen (SM-PAS) was superior on roentgenographic evaluation because there was a higher incidence and greater degree of improvement, with no instances of worsening. In all regimens, it was also noted on the roentgenograms that cavities became lost to view in only 4 to 20 per cent of those patients who had cavities when therapy started.

(c) The incidence of sputum "conversion" was highest for the combined intermittent regimen. No instances of bacterial resistance have yet been encountered on this regimen, compared to 75.9 per cent after daily streptomycin, 33.3 per cent after daily para-aminosalicylic acid, and 33.3 per cent after intermittent streptomycin regimens.

(d) The high incidence of toxic reactions (57.5 per cent) encountered when streptomycin was given daily decreased to 5 per cent when the drug was given every third day for a similar period. The incidence of toxicity when para-aminosalicylic acid was given daily was also 5 per cent. The higher incidence of toxic reactions (13.1 per cent) encountered when the two drugs were given together was not sufficient reason to preclude the use of the regimen except in 4 instances.

The patients were also evaluated after the 120-day treatment period. Since many had received additional streptomycin, para-aminosalicylic acid, or oper-

ative procedures, the only factor considered was worsening. This evaluation revealed a significant percentage of clinical, roentgenographic, and bacteriologic relapse. These observations suggest that longer courses of specific drug therapy may be warranted.

The phenomenon of a loss of bacterial resistance to one or the other of the drugs was encountered. This was marked in the daily para-aminosalicylic acid regimen and indicates that resistance to this agent may be less permanent than resistance to streptomycin.

From these observations it would seem that a combined intermittent regimen employing streptomycin every third day and para-aminosalicylic acid daily is the regimen of choice for periods up to four months when specific drug therapy is indicated for the treatment of nonmiliary pulmonary tuberculosis.

SUMARIO

Regímenes Intermitentes Combinados Empleando Estreptomicina y Acido Para-Aminosalicílico en el Tratamiento de la Tuberculosis Pulmonar

Un estudio comparativo de cuatro esquemas posológicos en un total de 283 enfermos fué llevado a cabo en el Centro Tuberculoso del Ejército de los Estados Unidos, en el Hospital Army Fitzsimons, durante los últimos cuatro años. En cada esquema, los enfermos fueron tratados por espacio de 120 días. Los cuatro esquemas comprendieron: 66 sujetos que recibieron estreptomicina, 1 ó 2 gm. diarios; 25 que recibieron ácido para-aminosalicílico, 12 gm. diarios; 97 que recibieron estreptomicina intermitentemente, 1 ó 2 gm. cada tres días; y 95 tratados con un régimen intermitente combinado: estreptomicina, 1 ó 2 gm. cada tres días, concomitantemente con ácido para-aminosalicílico, 12 gm. diarios.

Los grupos de enfermos en cada régimen fueron semejantes en cuanto a edad, sexo y raza, siendo también semejantes la duración, extensión y formas patológicas y clínicas de la enfermedad. Todos los sujetos tenían formas patológicas comprobadas de tuberculosis pulmonar, y ninguno había recibido antes farmacoterapia tuberculoestática. La tendencia roentgenográfica y la incidencia de cavernas eran parecidas y los cultivos mostráronse uniformemente sensibles a uno de los dos agentes o a ambos al iniciarse el tratamiento.

Los factores clínicos, radiográficos, bacteriológicos y tóxicos fueron justipreciados a los 120 días de tratamiento, y el análisis de los hallazgos reveló que:

(a) La respuesta clínica (en términos de reducción de la fiebre, reducción del volumen de esputo y aumento de peso) fué equivalente con los cuatro regímenes.

(b) Radiográficamente: El régimen intermitente combinado se mostró superior, por ser mayor la incidencia y la intensidad de la mejoría, sin casos de empeoramiento. Con todos los regímenes se notó también en las radiografías que las cavernas sólo se desvanecían en 4 a 20 por ciento de los enfermos que las tenían al iniciar la terapéutica.

(c) Bacteriológicamente: La incidencia de viraje del esputo alcanzó su máximo con el régimen intermitente combinado. No se han encontrado todavía casos de resistencia bacteriana con este régimen, comparado con: 75.9 por ciento con la

estreptomicina diaria, 33.3 por ciento con el ácido para-aminosalicílico diario y 33.3 por ciento con los regímenes intermitentes de estreptomicina.

(d) Reacción tóxica: La elevada proporción de reacciones tóxicas (57.5 por ciento) observada al administrar a diario la estreptomicina descendió a 5 por ciento al suministrar la droga cada tres días durante un período de tiempo semejante. La incidencia de toxicidad al administrar ácido para-aminosalicílico diariamente también fué de 5 por ciento. La mayor incidencia de reacciones tóxicas (13.1 por ciento) encontrada al administrar conjuntamente las dos drogas no constituyó razón suficiente para vedar el empleo del régimen, salvo en 4 casos.

Esos enfermos fueron también estudiados después de terminar el período de 120 días de tratamiento. Como muchos habían recibido después más estreptomicina, ácido para-aminosalicílico o cirugía, el único factor considerado fué el empeoramiento. Esta justipreciación reveló un porcentaje significativo de recidivas clínicas, radiológicas y bacteriológicas. Dichas observaciones indican que pueden estar justificadas series más largas de farmacoterapia específica.

Se observó un fenómeno de pérdida de la resistencia bacteriana. Esto fué pronunciado con el régimen diario de ácido para-aminosalicílico, indicando que la resistencia a esta droga puede ser menos permanente que a la estreptomicina.

Un régimen intermitente combinado que emplea la estreptomicina cada tres días y el ácido para-aminosalicílico cada día resulta, según estas observaciones, el régimen de elección para períodos hasta de cuatro meses cuando se halla indicada la farmacoterapia específica en la tuberculosis pulmonar no granúlica.

RESUME

Administration intermittente combinée avec emploi de streptomycine et d'acide para-amino salicylique dans le traitement de la tuberculose pulmonaire

Une étude comparative de quatre programmes de dosage chez 283 malades a été poursuivie au cours des quatre dernières années au Centre de la tuberculose de l'Armée des Etats-Unis, au "Fitzsimons Army Hospital". La durée du traitement des malades pour chaque programme a été de 120 jours.

Les quatre séries étaient constituées par: 66 malades traités par la streptomycine à la dose de 1 ou 2 g. par jour; 25 malades traités par l'acide para-aminosalicylique à la dose de 12 g. par jour; 97 malades traités par l'administration discontinue de streptomycine, 1 ou 2 g. tous les trois jours; et 95 malades traités par l'administration intermittente combinée de streptomycine, 1 ou 2 g. tous les trois jours et d'acide para-amino-salicylique, 12 g. par jour.

Les groupes de malades étudiés dans chaque série étaient semblables en ce qui concerne l'âge, le sexe et la race. La durée, l'étendue et le type pathologique de l'affection étaient également similaires. Tous les malades présentaient des manifestations pathologiques définies de tuberculose pulmonaire, ils n'avaient pas été soumis antérieurement à un traitement tuberculostatique. Les aspects radiologiques et l'incidence de lésions cavitaires étaient analogues et les cultures étaient uniformément sensibles à l'un et à l'autre des deux agents thérapeutiques au moment où le traitement a été institué.

Les facteurs clinique, radiologique, bactériologique et toxique ont été évalués après 120 jours de traitement. L'analyse des résultats obtenus ont montré que:

(a) la réaction clinique (en termes de réduction de la fièvre, de volume des crachats, et de reprise de poids) était équivalente dans les quatre séries.

(b) Les images radiologiques indiquaient que l'administration intermittente combinée donnait des résultats supérieurs, en raison de l'incidence de signes d'amélioration plus fréquente, et d'un degré plus élevé, sans exemple de signes d'aggravation. Il a été noté que, dans toutes les radiographies examinées, les cavernes existantes lorsque le traitement a commencé n'ont cessé d'être visibles que dans la proportion de 4 à 20 pour cent.

(c) L'examen bactériologique a montré que les modifications les plus marquées portant sur l'expectoration coincidaient avec l'administration intermittente combinée. Aucun exemple de résistance bactérienne n'a été constaté avec ce mode d'administration, par opposition aux 75,9 pour cent observés avec l'administration quotidienne de streptomycine, 33,3 pour cent après l'administration quotidienne d'acide para-amino-salicylique et 33,3 pour cent après l'administration discontinue de streptomycine.

(d) Réactions de toxicité. L'incidence élevée des phénomènes toxiques (57,5 pour cent) constatés avec l'administration quotidienne de streptomycine s'est abaissée jusqu'à 5 pour cent quand l'antibiotique a été donné tous les trois jours pendant un temps comparable. En ce qui concerne l'administration quotidienne de l'acide para-amino-salicylique, le taux des réactions toxiques a été également de 5 pour cent. L'incidence plus élevée des réactions toxiques (13,1 pour cent) rencontrée quand les deux médications ont été associées n'a pas été considérée comme suffisante pour prévenir l'application de ce mode d'administration, sauf dans 4 cas.

Ces patients ont été également étudiés après un traitement d'une durée de 120 jours. Etant donné que beaucoup d'entre eux avaient reçu une quantité supplémentaire de streptomycine, d'acide para-amino-salicylique et des soins chirurgicaux, le seul facteur considéré était l'aggravation. L'évaluation de ce facteur a révélé une proportion élevée de rechutes d'ordre clinique, radiologique et bactériologique. Ces observations suggèrent qu'il y aurait lieu de prolonger la durée des séries de traitement avec la médication spécifique.

La disparition de la résistance bactérienne a été un phénomène observé. Ceci a été particulièrement marqué avec l'administration quotidienne d'acide para-amino-salicylique et indique que la résistance à ce composé pourrait être moins permanente que la résistance à la streptomycine.

L'administration intermittente combinée en donnant la streptomycine tous les trois jours et l'acide para-amino-salicylique tous les jours, est considérée selon l'expérience des auteurs comme le traitement de choix quand les séries de thérapie spécifique peuvent s'étendre sur une période de quatre mois, comme il est indiqué dans les cas de tuberculose pulmonaire non miliaire.

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NEUROTOXICITY OF DIHYDROSTREPTOMYCIN[1,2]

Effects of Longer-term Therapy

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INTRODUCTION

By early 1949 adequate evidence had been reported from various sources (1, 2) to indicate that combined therapy with both a streptomycin drug and para-aminosalicylic acid, administered concurrently, could be expected to exert a considerably more prolonged therapeutic effect against pulmonary tuberculosis than either streptomycin or dihydrostreptomycin alone. Included in the study of combined chemotherapy at the Laurel Heights Sanatorium was a selected group of patients who received treatment for prolonged periods of six months or more. Therapeutic results and bacteriologic data from this study will be reported in another communication. The present report is concerned only with the incidence of significant and sometimes serious toxic effects which prolonged chemotherapy has entailed.

PLAN OF INVESTIGATION

Data are presented regarding the auditory and vestibular disturbances resulting from the use of streptomycin or dihydrostreptomycin in 22 patients (14 female, 8 male) treated for three months, and in 33 patients (17 female, 16 male) who received treatment for six consecutive months or longer. For testing the labyrinthine function a modified Kobrak caloric test, using 20 cc. of ice water (40 cc. in patients unresponsive to 20 cc. of ice water) in each auditory canal, was performed before and upon completion of treatment. Air-conduction audiograms[3] were done before, during, and upon completion of treatment. A significant auditory impairment was deemed to have occurred when post-treatment audiograms demonstrated a loss of 20 decibels or greater in at least two different frequencies as compared to the pre-treatment audiogram.

Drug Dosage

Forty-seven of the 55 patients received 10 gm. of para-aminosalicylic acid administered as the sodium salt by mouth daily during their course of treatment. Because of frequent loose bowel movements, the daily dosage was reduced to 5 to 7 gm. in the remaining 8 patients.

Streptomycin sulfate given in one daily injection was the streptomycin salt used. Patients receiving dihydrostreptomycin received either the hydrochloride

[1] From Laurel Heights Tuberculosis Sanatorium, Shelton, Connecticut.

[2] This study was aided by grants from the Division of Research Grants and Fellowships of the National Institutes of Health, Public Health Service.

[3] The audiometer was manufactured by the Audio Development Company, Minneapolis, Minnesota.

or sulfate salt, or both, during their course, the daily dose being given in one injection.

The daily dose of streptomycin or dihydrostreptomycin was based on the patient's weight as follows:

Less than 90 pounds	0.75 gm.
Between 90 and 119 pounds	1.0 gm.
Between 120 and 150 pounds	1.2 gm.
More than 150 pounds	1.5 gm.

If the patient's weight changed during treatment, the daily dose was changed accordingly. The dose-weight scale was employed as a convenient guide for administering a daily dose of roughly 20 mg. per kg. of body weight. Regardless of weight, however, no patient received more than 1.5 gm. daily of either streptomycin drug.

Renal Function

Frequent routine urinalyses were done before and during treatment. If any abnormality was noted, a blood nonprotein nitrogen determination and a phenolsulfonphthalein renal excretion test were done. In those patients who manifested audiometric loss, no evidence of impaired renal function was noted with the tests used.

OBSERVATIONS

Labyrinthine Function

In bed patients the caloric test is a more sensitive and accurate indicator of dysfunction than such symptoms as dizziness and ataxia. Therefore, for brevity, only the results of caloric tests will be tabulated (table 1), although most of the patients showing significant loss of response to caloric stimulation also had definite symptoms.

As may be seen in table 1, only one of 11 patients who received dihydrostreptomycin and para-aminosalicylic acid (PAS) for three months had any diminution in the caloric response; whereas 7 of 11 patients who received streptomycin and PAS for a similar period had evidence of diminished or absent caloric response at the end of treatment. Among 16 patients treated for six months or longer with dihydrostreptomycin and PAS, 6 had altered caloric response at the end of treatment. Ten of 12 patients who received streptomycin and PAS for a similar period had altered caloric response upon completion of treatment. Subsequent caloric testing of the patients treated three months only has shown complete return to normal of the caloric response in 7 of the 8 patients who had suffered impairment or loss. Follow-up data are not yet available on the patients treated for six months or longer.

Auditory Function

Audiometry: Data based on audiograms performed as previously described are presented in table 2. Of the 11 patients who received dihydrostreptomycin and

PAS for only three months, none had evidence of auditory impairment at the end of treatment. Within three months after completion of therapy, however, there was significant auditory impairment in 3 patients. Similar results have been obtained by Allison, Volk, and Vitagliano (3) and Romansky and his associates

TABLE 1

Caloric Tests of Labyrinthine Function Performed at the End of Treatment on Patients Treated with Dihydrostreptomycin-PAS or Streptomycin-PAS for Three or Six Months

DURATION OF CHEMOTHERAPY	DRUG USED	PATIENT TOTAL	CALORIC RESPONSE		
			Normal	Hyposensitive	Lost†
3 months	*Dihydrostreptomycin	11	10	1	0
	Streptomycin sulfate	11	4	5	2
6 months	*Dihydrostreptomycin	16	10	4	2
	Streptomycin sulfate	12	2	5	5

* The dihydrostreptomycin used was either the sulfate or hydrochloride salt, or *both*, in each patient.

† If there was no response to 40 cc. of ice water, the caloric response was considered lost.

TABLE 2

Results of Audiometric Determinations (Air Conduction) Performed after Three or Six Months' Treatment with Dihydrostreptomycin-PAS or Streptomycin-PAS

An Impairment of 20 Decibels or More in Two Different Frequencies is Considered a Significant Loss

DURATION OF CHEMOTHERAPY	DRUG USED	PATIENT TOTAL	AUDIOMETRY		
			No loss	Immediate loss	Delayed loss
3 months	*Dihydrostreptomycin	11	8	0	3
	Streptomycin	11	11	0	0
6 months	*Dihydrostreptomycin	21	5	16	0
	Streptomycin	12	12	0	0

* The dihydrostreptomycin used was either the sulfate or hydrochloride salt, or *both*, in each patient.

(4) among patients receiving higher daily doses of dihydrostreptomycin alone. The latter investigators also reported the occurrence of hearing loss in 2 patients who received only 1.0 gm. of streptomycin daily.

In the present study, 16 of 21 patients who received dihydrostreptomycin and PAS for six months had significant auditory impairment. In contrast, no patient in the two groups who received streptomycin and PAS had impairment of audi-

tion. Thus far, impairment of hearing had been persistent in all of the affected patients, with no instance of improvement after chemotherapy was discontinued.

Symptoms: Among the 19 patients who received dihydrostreptomycin and PAS and who had audiometric loss, 2 are now totally deaf for spoken voice; 3 have moderate-to-severe impairment; 4 have slight impairment; 3 have slight but insignificant impairment; and 7 believe that there has been no change in their hearing ability.

When patients had some audiometric loss in the higher frequencies before treatment, the additional impairment resulting from neurotoxicity of dihydrostreptomycin often resulted in marked auditory impairment. However, 4 of 8 patients with completely normal audiograms before therapy had difficulty in hearing spoken voice upon completion of treatment and in one instance the impairment was marked.

TABLE 3

Age Grouping of the 21 Patients Who Received Dihydrostreptomycin and Para-aminosalicylic Acid for Six Months or More

AGES	20-29	30-39	40-49	50-59	60-69	MORE THAN 70
Total patients	7	1	5	3	3	2
Patients with audiometric loss	3	1	4	3	3	2

The other symptom worth noting is tinnitus. This occurred at one time or another in all of the patients with significant hearing loss, although its severity and constancy varied considerably.

Age: The ages of the patients with delayed impaired audition after three months' therapy were 33, 44, and 49 years. Ages of those affected in the six-month treatment group are given in table 3. It will be noted that of the 13 patients more than 39 years of age, 12 suffered auditory impairment; and of 8 patients less than 39 years of age, 4 had impaired auditory function.

Sex: The six-month dihydrostreptomycin group was composed of 11 males all of whom had auditory loss and of 10 females of whom 5 had loss. The 3 losses, all in females, in the three-month group occurred in a group comprised of 2 men and 9 women.

Actual dosage: As stated before, the dosage of antibiotic used was based on approximately 20 mg. of drug per kg. of body weight. The actual daily dose used in the 3 patients who had delayed loss after three months' therapy was 1.0 gm. of dihydrostreptomycin. Of the 16 patients with loss in the six-month group, 3 received 1.0 gm. daily; 8 received 1.2 gm. daily; and 5 received 1.5 gm. daily.

Dissociation of auditory and vestibular toxicity: Of interest is the finding that in several of the patients who developed severe auditory loss the caloric test was entirely normal after six months of therapy.

DISCUSSION

Since all patients in this study received para-aminosalicylic acid, it is presumed that any difference in neurotoxicity noted can be attributed to the antibiotic used, i.e., streptomycin sulfate or dihydrostreptomycin.

The vestibular disturbances resulting from streptomycin are well known, and the experiences in this study are no different in kind from those previously reported by many investigators. It should be noted, however, that complete loss of response to caloric stimulation was considerably more frequent in the patients treated with streptomycin and PAS for six months or longer than in those treated for only three months; symptoms also were likely to be more disturbing in the long-term treatment group. It appears, therefore, that prolongation of treatment with streptomycin in the doses employed in this study has significantly increased the patient's liability to the more severe degrees of dysfunction of the labyrinth. Whether this damage is reversible remains to be determined, but past experience with other patients showing no response to caloric stimulation is not encouraging in so far as actual return of labyrinthine function is concerned.

That streptomycin has rarely resulted in impaired hearing in nonmeningitic patients treated with this drug for four months or less has long been recognized. Experience in the present study further confirms the fact that streptomycin given intramuscularly in the doses generally employed has little toxic effect upon the auditory mechanism. Even among the patients treated with streptomycin and PAS for periods of six months or longer (including several patients treated from nine to twelve months) not a single instance of significant hearing loss occurred.

With regard to dihydrostreptomycin, the subject of neurotoxicity remains somewhat confused. The early toxicity studies by Edison and her associates (5), by Hobson and his associates (6), and by Hinshaw and the Mayo Clinic group (11) stressed the fact that dihydrostreptomycin was far less toxic for the labyrinth than streptomycin. The accuracy of this conclusion has been abundantly confirmed by subsequent experience and is thoroughly in line with the experience reported in the present study.

The toxicity of dihydrostreptomycin for the auditory apparatus, on the contrary, remains unsettled and is a topic on which very divergent opinions have been expressed. For example, in the early study of Hobson and his associates, auditory impairment on large doses (5.0 gm. daily) was noted, but these investigators concluded that, although dihydrostreptomycin may cause damage to the auditory apparatus, it is no more toxic in this respect than streptomycin and, in all probability, is less so. Subsequently, Romansky, Glorig, and their associates (4, 7), and Allison, Volk, and Vitagliano (3) reported a very disturbing incidence of deafness in patients treated with dihydrostreptomycin in daily doses of 2.0 gm. or more, and pointed out that this auditory impairment was often delayed, appearing after treatment had been stopped. It is to be noted that the deafness reported by these investigators occurred largely in patients receiving the relatively high daily doses of 2.0 to 5.0 gm., and many physicians continued to hope

that, with smaller doses, deafness would not be a problem. Subsequently, however, D'Esopo (8) reported significant loss of hearing in 5 patients who had received 1.0 gm. of dihydrostreptomycin daily for periods of twenty-nine weeks or longer, and clearly pointed out that dihydrostreptomycin hydrochloride is distinctly more toxic for hearing than is streptomycin, especially when treatment is prolonged.

In spite of these warnings, which were further discussed at the Ninth Streptomycin Conference of the Army, Navy, and Veterans Administration, the concern of these investigators was not shared by some of the other participants. It was pointed out at this conference that the toxicity tables, which contained data on cases treated in various participating hospitals, did not reflect a significant difference between streptomycin and dihydrostreptomycin in their effect upon hearing. In fact, doubt was expressed that the tables lent any support whatsoever to the fears that dihydrostreptomycin might prove to be toxic for the auditory nerve. It shou'd be emphasized, however, that the tables referred to contained no data on patients treated with dihydrostreptomycin for longer than ninety days.

In the present study, the toxicity for the auditory apparatus of dihydrostreptomycin in doses of approximately 20 mg. per kg. of body weight (total doses of 1.0 to 1.5 gm. daily) has been further demonstrated. While significant loss of hearing occurred in a few patients treated for only three months, the loss observed after six months or more of treatment occurred far more frequently and was generally much more severe and alarming in the patients affected. Several patients are now quite hard of hearing and 2 are "stone" deaf. Furthermore, none of the patients with impaired hearing has yet shown any improvement after treatment was discontinued.

The pattern of hearing loss in these patients is typically illustrated in figures 1 and 2. The higher frequencies are lost first and then progressive loss may occur in the lower-spoken voice frequencies. If previous impairment has taken place from other causes, further loss from the drug may be disastrous to hearing.

The minimum requirement for significant loss of hearing audiometrically has been arbitrarily placed in this report at 20 decibels in two different frequencies. However, one patient in the three-month treatment group and 6 in the long-term group had losses of 40 decibels or more and in some patients all frequencies were eventually involved. Unless audiograms are performed routinely, the early stages of impaired hearing are likely to be missed.

Carr and his associates (9) have reported on neurotoxic reactions from dihydrostreptomycin with a daily dosage of 2.0 gm. or more. The toxic reactions were attributed to serum levels of dihydrostreptomycin in excess of 60 γ per cc., due to high dosage or impaired renal function or both. In the present study, dihydrostreptomycin levels in the blood serum were not determined. On the basis of the renal function tests performed, however, there was no evidence of impaired function in the patients with toxic manifestations reported here, and daily doses were moderate.

It is clear from the data presented that the dihydrostreptomycin employed in

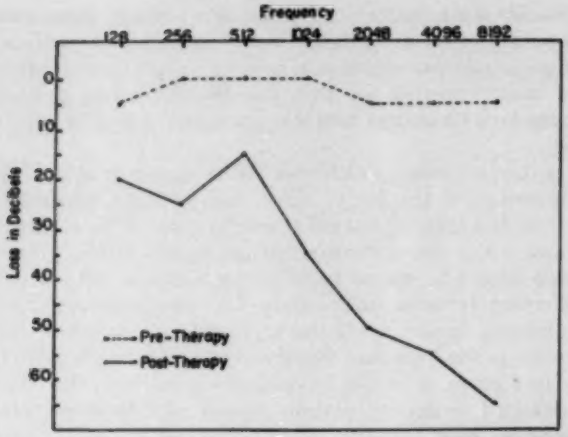

FIG. 1. Air-conduction audiograms of right ear before and after six months' treatment with dihydrostreptomycin (1.2 gm. daily) and para-aminosalicylic acid (10 gm. daily). Similar changes occurred in the left ear. Audition is definitely impaired for spoken voice.

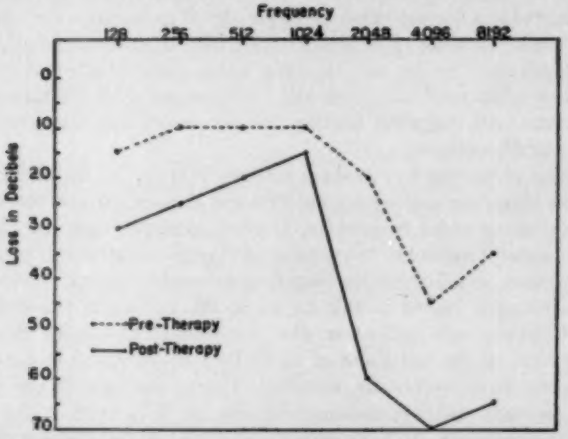

FIG. 2. Air-conduction audiograms, left ear, before and after six months' treatment with dihydrostreptomycin (1.0 gm. daily) and para-aminosalicylic acid (10 gm. daily). Similar changes occurred in the right ear. Although this patient had hearing loss in the high frequencies before therapy, the additional impairment from DHSM has resulted in definitely impaired hearing for spoken voice.

this study was far more toxic for hearing than the streptomycin which was used. It is not clear whether or not all of the several lots and brands of dihydrostreptomycin used were equally toxic in this respect. On the basis of experimental data

in cats, Hawkins (10) concluded that dihydrostreptomycin hydrochloride produced more auditory disturbance than dihydrostreptomycin sulfate, and attributed the difference not to any inherent difference in the two salts themselves, but to the much greater proportion of unspecified impurities present in the preparation of dihydrostreptomycin hydrochloride which he employed. Hawkins concluded that these impurities may well be responsible for the loss of hearing observed in patients, and some clinicians also have suggested that the effect upon hearing may be greatly reduced or eliminated if the purer sulfate salt is employed.

In the present report, all references to streptomycin and dihydrostreptomycin and to their specific salts refer, of course, not to pure chemicals but to the commercial preparations actually administered to patients. Determination of whether the toxic manifestations observed in these patients were due to impurities or to the active salts themselves is clearly beyond the scope of this study. With regard to the relative toxicity of dihydrostreptomycin hydrochloride and dihydrostreptomycin sulfate, as furnished commercially, the following observations are, however, of interest.

Certainly dihydrostreptomycin hydrochloride is culpable, for the patients with impaired hearing reported by Romansky and Glorig and by D'Esopo had all received only the hydrochloride salt, as did some of Allison's patients. Moreover, the hydrochloride was the only salt of dihydrostreptomycin employed in all but one of the patients in the three-month treatment group reported in table 2.

In the group treated with dihydrostreptomycin and PAS continuously for six months or longer and included in the present study, 2 patients received the hydrochloride salt throughout, and both sustained significant loss of hearing. The remaining 19 patients in this group received the hydrochloride salt for at least part of their course of treatment (4 months in one, 3.5 months in one, 3 months or less in 17), the sulfate salt thereafter. It is entirely possible, therefore, that loss of hearing in this group also is the result solely of the hydrochloride salt. If such were the case, however, and if dihydrostreptomycin sulfate were completely innocuous to the auditory mechanism, the incidence of impaired hearing in this group, at least among the 17 patients who for three months or less received dihydrostreptomycin hydrochloride, should be no greater than was observed in the three-month treatment group reported in table 2. That the incidence is, in fact, much greater (70 per cent versus 27 per cent) suggests strongly that the prolongation of treatment, during which only the sulfate salt of dihydrostreptomycin was employed, is the factor responsible.

One further observation appears pertinent to this discussion. Certain other patients at Laurel Heights have also been treated with dihydrostreptomycin and PAS, but not as a part of the particular study reported here. Data on these "ordinary treatment" cases are not as complete as on the special study group. In the "ordinary treatment" group, however, are 8 patients who received this combination of drugs continuously for periods of six months or longer but to whom dihydrostreptomycin was administered as the hydrochloride salt for thirty days or less and as the sulfate salt for the remainder of their course. The daily

dose was not in excess of that employed in the study group. Among these 8 patients, significant loss of hearing either audiometrically or clinically, or both, was observed in 4. Only one of these 4 patients had received any dihydrostreptomycin hydrochloride at all; the other 3 had received dihydrostreptomycin only as the sulfate salt. The hearing loss observed in these last 3 patients was in no instance severe, and was noticeable clinically in only one. Nevertheless this experience provides further reason for concern regarding the effect upon hearing, not only of dihydrostreptomycin hydrochloride, but of dihydrostreptomycin sulfate as well.

The toxic manifestations reported here are obviously neither new nor unknown. The purpose of the present report principally is to emphasize the fact that both the incidence and severity of these toxic manifestations are likely to increase to a very significant degree when the streptomycin drugs are administered continuously for long periods of time. This hazard may, of course, be far outweighed by the advantages of long-term combined chemotherapy in many tuberculous patients, and it is by no means implied that long-term therapy should not be employed. The hazard does, however, deserve careful consideration in every patient for whom prolonged use of chemotherapy is contemplated, and should be weighed with special care in patients in the older age groups where compensation for loss of labyrinthine function is sometimes difficult and where serious loss of hearing has occurred most frequently.

Especially notable in the present report is the significant loss of hearing observed in a high percentage of patients treated with dihydrostreptomycin and PAS for six months or longer, contrasted with the absence of significant hearing loss in the group of patients for whom streptomycin and PAS were similarly employed. On the basis of this experience there is no doubt that this hearing loss is generally far more distressing in the patients affected than is the loss of labyrinthine function which has been the principal problem when streptomycin was used. Compensation even for complete loss of labyrinthine function is usually satisfactory and is often fairly rapid, although exceptions to this rule do occur.

As a consequence of the experience herein reported, the present policy at Laurel Heights is to prefer streptomycin to dihydrostreptomycin and to employ a maximum daily dose of 1.0 gm. Dihydrostreptomycin is now used only in the occasional patient who is allergic to streptomycin, or for whom the avoidance of labyrinthine dysfunction is deemed unusually important because of some pre-existing impairment to locomotion from previous injury or disease. Moreover, response of each patient to caloric stimulation (and also to audiometry when dihydrostreptomycin is employed) is tested periodically during treatment so that evidence of toxicity may be detected early. When evidence of beginning toxicity occurs, this hazard is weighed against the patient's need for further chemotherapy and the treatment regimen (duration, dosage, the particular drugs employed, and plans for collateral therapy) is adjusted accordingly. Among the procedures now being tried in an effort to reduce the toxicity of long-term combined chemotherapy is the administration of the streptomycin drug twice a week instead of daily (12).

Unfortunately, most of the patients treated with dihydrostreptomycin received, during their course of treatment, more than one lot of this drug and in many instances several different brands and both salts were employed. Furthermore, the loss of hearing observed in this group was irregular both in incidence and severity, and none of the specific products of dihydrostreptomycin employed were analyzed for potency and purity. It is apparent, therefore, that correlation of toxicity with the purity of the particular product employed is impossible, and that clear-cut evidence regarding the relative toxicity for hearing of dihydrostreptomycin sulfate and dihydrostreptomycin hydrochloride is notably lacking in this study. All of the patients who are seriously deaf received at least some dihydrostreptomycin hydrochloride, and it is entirely possible that the toxicity of the purer sulfate salt is much less than that of the hydrochloride which, according to Hawkins (10), is a relatively impure drug. More definitive studies of dihydrostreptomycin sulfate have been undertaken by several investigators. If these studies demonstrate that the present concern for the hazard of deafness applies only to dihydrostreptomycin hydrochloride or to other impure preparations of dihydrostreptomycin, then present policy at Laurel Heights will have to be revised accordingly. Nevertheless, evidence has been presented which suggests that the dihydrostreptomycin sulfate employed in the present study was, at best, not innocuous to hearing. Until clear evidence to the contrary is available, it seems safest to assume that significant loss of hearing may result from prolonged use of dihydrostreptomycin in any form.

SUMMARY

The toxic effects of streptomycin and of dihydrostreptomycin upon the labyrinthine and the auditory mechanisms have been studied in a group of 55 patients treated with one or the other of these drugs together with para-aminosalicylic acid concurrently. It was noted that these toxic manifestations increased to a very considerable degree when patients were treated continuously for six months or more with daily doses of 1.5 gm. or less of the streptomycin drug used.

The principal toxic manifestation in the patients who received streptomycin was impairment of labyrinthine function. Complete loss of response to caloric stimulation occurred in 5 of 12 patients treated with streptomycin and PAS for six months or more. On the other hand, none of the streptomycin-treated patients has yet shown significant loss of hearing, regardless of the duration of therapy.

The principal toxic manifestation in the patients who received dihydrostreptomycin was impairment of hearing. Comparison of pre- and post-treatment audiograms demonstrated significant hearing loss in 3 of 11 patients treated with dihydrostreptomycin and PAS for three months, and in 16 of 21 patients treated for six months or longer. Moreover, significant deafness is apparent clinically in 12 of these patients, 2 of whom are "stone" deaf.

It is possible that dihydrostreptomycin sulfate is much less toxic for hearing than dihydrostreptomycin hydrochloride. If so, this difference is presumably due to the higher proportion of impurities present in commercial preparations of

the hydrochloride salt. Data from the present study do not provide decisive evidence on this question. Until such data are available from other studies, however, there seem to be good reasons for assuming that significant impairment of hearing may result from either salt of dihydrostreptomycin.

In the patients affected, impaired hearing has generally been a far more distressing sequela of treatment than impaired labyrinthine function. Following cessation of chemotherapy, no patient has yet shown improvement in hearing, whereas eventual compensation for loss of labyrinthine function has usually been satisfactory. Hence, with certain exceptions, streptomycin is now preferred to dihydrostreptomycin, especially in patients for whom prolonged courses of combined chemotherapy are contemplated.

SUMARIO

Neurotoxicidad de la Dihidroestreptomicina

Los efectos tóxicos de la estreptomicina y la dihidroestreptomicina sobre el laberinto y el mecanismo auditivo fueron estudiados en un grupo de 55 enfermos tratados con una u otra de dichas drogas concurrentemente con el ácido para-aminosalicílico. Observóse que las manifestaciones tóxicas aumentaban considerablemente cuando se trataba continuamente a los enfermos por espacio de seis meses o más con dosis diarias de 1.5 gm. o menos de la droga estreptomicínica usada.

La principal manifestación tóxica en los enfermos que recibieron estreptomicina consistió en disfunción del laberinto. Sobrevino pérdida total de la respuesta a la excitación calórica en 5 de 12 enfermos tratados con estreptomicina y PAS por espacio de seis meses o más. En cambio, ninguno de los tratados con estreptomicina ha revelado todavía mayor pérdida del oído, independientemente de la duración de la terapéutica.

La principal manifestación tóxica en los enfermos que recibieron dihidroestreptomicina consistió en disminución de la audición. La comparación de los audiogramas tomados antes y después del tratamiento mostró pérdida significativa de la audición en 3 de 11 enfermos tratados con dihidroestreptomicina y PAS durante tres meses y en 16 de 21 tratados durante seis meses o más. Además, existe sordera clínicamente aparente en 12 de cichos sujetos, 2 de los cuales están sordos de remate.

Es posible que el sulfato de dihidroestreptomicina sea mucho menos tóxico que el clorhidrato para el oído. Los datos derivados del estudio actual no suministran prueba fehaciente sobre este punto. Hasta que otros estudios aporten tales datos, parece que hay buenas razones para suponer que, con una u otra sal de la dihidroestreptomicina, puede ocurrir pérdida importante de la audición.

En los enfermos afectados, la torpeza de oído ha constituído una secuela mucho más molesta del tratamiento que la disfunción del laberinto. Después de cesar el tratamiento, ningún paciente ha revelado todavía mejoramiento de la audición, en tanto que, por lo general, ha solido ser satisfactoria la compensación eventual de la pérdida de la función laberíntica. Por esto, con ciertas excepciones,

prefiérese hoy día la estreptomicina a la dihidroestreptomicina, máxime en los enfermos a quienes se proyecta administrar tandas prolongadas de quimioterapia combinada.

RESUME

Neurotoxicité de la Dihydrostreptomycine

L'action toxique de la streptomycine et de la dihydrostreptomycine sur le labyrinthe et le système auditif a été étudiée sur un groupe de 55 malades traités avec l'une ou l'autre de ces substances en association avec l'acide para-aminosalycylique. Il a été constaté que ces manifestations toxiques augmentaient considérablement d'importance quand la durée d'administration continue d'une préparation représentant 1 g. 50 ou moins de streptomycine par jour atteignait six mois ou plus.

La principale manifestation de toxicité observée chez les malades traités par la streptomycine a été l'altération de la fonction labyrinthique. La disparition complète de la réaction vestibulaire thermique a été observée chez 5 malades sur les 12 cas traités par la streptomycine et le P.A.S. pendant six mois ou plus. D'autre part, jusqu'à présent, aucun des malades traités par la streptomycine n'a présenté de perte appréciable de l'audition quelque 'ait pu être la durée du traitement.

La principale manifestation toxique observée chez les malades traités par la dihydrostreptomycine a été l'altération de l'audition. La comparaison des audiogrammes, avant et après le traitement, a montré une perte appréciable de l'audition chez 3 des 11 malades traités par la dihydrostreptomycine et le P.A.S. pendant trois mois, ainsi que chez 16 malades sur les 21 cas traités pendant six mois ou plus. De plus, une surdité importante est constatée cliniquement chez 12 de ces malades; 2 d'entre eux sont complètement sourds.

Il est possible que le sulfate de dihydrostreptomycine soit moins nocif pour l'audition que ne l'est le chlorhydrate de dihydrostreptomycine . Les faits observés dans cette étude ne fournissent pas de preuves sur ce point. Toutefois, jusqu'à ce que ces données soient obtenues à la suite d'autres études, il y a toutes raisons d'envisager la possibilité d'une altération de l'audition succédant à l'emploi de l'un ou de l'autre sel de dihydrostreptomycine.

L'altération de l'audition s'est montrée en général une séquelle plus difficile à supporter par les malades que l'altération de la fonction labyrinthique. Alors qu'on a parfois observé, après l'arrêt de la chimiothérapie, une certaine compensation de l'altération de la fonction labyrinthique, jusqu'à présent l'amélioration de l'audition n'a été constatée chez aucun malade. En conséquence, avec quelques exceptions, la streptomycine est actuellement préférée à la dihydrostretomycine et en particulier dans les cas ou une chimiothérapie mixte est envisagée.

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THERAPEUTIC PNEUMOTHORAX IN MIDDLE-AGED AND ELDERLY PATIENTS[1]

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INTRODUCTION

Methods of treatment of pulmonary tuberculosis, especially the different forms of collapse therapy, were designed originally for the young tuberculous patient. As a consequence, the experience gained in the use of these methods deals in the main with their indications and results in patients less than 40 years of age. While at the present time and especially in this country the mortality of tuberculosis is decreasing, a marked relative increase in the older age groups is noted (1, 2, 3). Whatever its cause may be, this change in the epidemiologic picture forces the clinician to select and adapt methods of treatment suitable for older patients.

According to reports in the literature, therapeutic pneumothorax has been used infrequently in the aged. Rubin (4) mentions good results of pneumothorax treatment in a diabetic woman, 56 years of age, in whom hemoptysis could be controlled; and in a man, 70 years of age, who had tuberculosis and diabetes. Freeman and Heiken (5) have reported 52 cases of pulmonary tuberculosis in patients more than 60 years of age studied at autopsy. In 4 of the patients, induction of pneumothorax had been attempted. Pneumothorax had been successful in one patient, hydropneumothorax developed in another, and in 2 patients the induction had not been possible. Deane (6) treated a 71-year-old woman and a 59-year-old man successfully with pneumothorax; these patients were well at an age of 78 and 62 years, respectively. Amberson (7) points out that the inelasticity of an emphysematous lung in the aged may prevent a prompt collapse of the lung; furthermore, impairment of pulmonary function and dyspnea occur more frequently in the elderly, and may be contraindications to the induction of a pneumothorax.

Because of the scarcity of reports and the probability that pneumothorax treatment will become more frequent in the higher age group, the following study was undertaken. It comprises all patients above the age of 50 in whom pneumothorax was induced for the treatment of pulmonary tuberculosis during the period from 1939 to 1945.

COMPOSITION OF CLINICAL SERIES

There were 20 patients above the age of 50 years in whom a pneumothorax was induced in the years between 1939 and 1945 at Montefiore Hospital and at the Montefiore Country Sanatorium, Bedford Hills, New York. Three were excluded from further consideration because pneumothorax treatment was dis-

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continued after two weeks or less. In 2 patients this was done because of inadequacy of the space; and in one, because of dyspnea.

Among the remaining 17 patients were 11 males and 6 females whose ages ranged from 50 to 64 years. The age distribution is shown in table 1. Fourteen patients had far advanced pulmonary tuberculosis; in 3 the disease was moderately advanced. The disease was unilateral in 4 patients. Bilateral disease was found among 13 patients, and bilateral pneumothorax was given to 4 patients in this group. The character of the disease was considered caseous-pneumonic in one patient; this patient died. In all of the other patients fibrocaseous pulmonary tuberculosis was noted, and every patient had tubercle bacilli in his sputum.

Eleven of the 17 patients had other diseases in addition to pulmonary tuberculosis: 10 (7 male, 3 female), diabetes mellitus; 3 (1 male, 2 female), arteriosclerotic and hypertensive cardiovascular disease; 1 (male), Kimmelsteil-Wilson syndrome; 1 (male), bronchial asthma and emphysema; and 1 (male), sarcoma of the thigh. Five of these patients had two complicating diseases, diabetes

TABLE 1

Pneumothorax Therapy in Middle-aged and Elderly Patients

Age of Patients at the Time of Pneumothorax Induction

AGE	NUMBER OF PATIENTS	MALE	FEMALE
years			
50 to 54	8	5	3
55 to 59	7	4	3
60 to 64	2	2	—
Total	17	11	6

mellitus and hypertension were present in 3, diabetes mellitus and arteriosclerosis in one, diabetes mellitus and sarcoma of the thigh in one.

RESULTS

In evaluating the results of treatment, it was convenient to divide the patients into three groups: (*A*) discharged with sputum free of tubercle bacilli on microscopic examination of stained concentrated specimens; (*B*) discharged with sputum containing tubercle bacilli on similar examination of unconcentrated specimens; and (*C*) patients who died in the hospital.

A summary of the conditions of the patients at the time of their discharge from the hospital is recorded in table 2.

In *Group A* (7 patients discharged from hospital free of tubercle bacilli in the sputum), pneumothorax treatment was effective in 5 patients. In 2 of the patients, the pneumothorax had to be discontinued prematurely because of empyema. These 2 patients recovered, however, and could be discharged with arrested or apparently arrested tuberculosis. In the sixth patient, pneumothorax treatment was probably of temporary benefit, as the lesions on the more involved

side were controlled until the contralateral lesions had stabilized sufficiently to make thoracoplasty possible. In the seventh case pneumothorax was clearly ineffective, but the patient recovered and was discharged with arrested tuberculosis following a prolonged period of bed rest.

Obviously, pneumothorax was not completely effective in all of the 5 patients of *Group B* who were discharged with bacilliferous sputum.

TABLE 2

Pneumothorax Therapy in Middle-aged and Elderly Patients
Clinical Status of Patients at Time of Hospital Discharge

		PNEUMOTHORAX MAINTAINED	PNEUMOTHORAX DISCONTINUED	PNEUMOTHORAX DISCONTINUED, THORACOPLASTY	TOTAL NUMBER
Group A Sputum free of tubercle bacilli in concentrated specimens	Arrested	2	2	1	5
	Apparently arrested	—	1	—	1
	Quiescent	1	—	—	1
Group B Sputum containing tubercle bacilli in unconcentrated specimens	Quiescent	—	1	1	2
	Active	—	3	—	3

TABLE 3

Pneumothorax Therapy in Middle-aged and Elderly Patients
Clinical Status at Time of Latest Follow-up Information

STATUS	*Group A* SPUTUM FREE OF TUBERCLE BACILLI IN CONCENTRATED SPECIMENS	*Group B* SPUTUM CONTAINING TUBERCLE BACILLI IN UNCONCENTRATED SPECIMENS	TOTAL
Arrested	3	0	3
Quiescent ("good chronics")	0	3	3
Dead	3	1	4
Not traced	1	1	2

The clinical status of the patients in both *Group A* and *Group B* at the time of the latest follow-up information available is summarized in table 3. Excluding 2 patients who could not be traced and one patient who died one month following discharge, the follow-up period varied between six months and seventy-nine months, with an average of forty-six months. The cause of death in the different groups may be seen in table 4.

On the whole, patients discharged with sputum free of tubercle bacilli (*Group A*) tended to maintain, or even to reach, the "arrested" status after discharge.

One patient in *Group A* died one month after discharge under unknown circumstances. The other 2 deaths in this group were due to reactivation of disease after several years of apparently good health. Though the number of patients is small, these results are similar to those usually observed in younger patients.

TABLE 4

Causes of Death in Series of Middle-aged and Elderly Patients Treated with Pneumothorax

		PROGRESSIVE TUBERCULOSIS	PROGRESSIVE TUBERCULOSIS AND DIABETES	PNEUMOTHORAX COMPLICATIONS	UNKNOWN
After discharge	*Group A* Sputum free of tubercle bacilli in concentrated specimens	1*	1†	0	1‡
	Group B Sputum containing tubercle bacilli in unconcentrated specimens	1§	0	0	0
In hospital	*Group C*	0	1	4	0
Total		2	2	4	1

* Six and one-half years after discharge.
† Four and one-half years after discharge.
‡ One month after discharge.
§ Three years after discharge.

TABLE 5

Correlation of Latest Clinical Findings and Duration of Pneumothorax in Series of Middle-aged and Elderly Patients Treated with Pneumothorax

DURATION OF PNEUMOTHORAX	CLINICAL STATUS			
	Arrested	Quiescent	Died	Not traced
years				
Less than 1	1	3	6	1
1 to 2	0	0	3	1
2 to 3	1	0	0	0
3 to 4	0	0	0	0
More than 4	1	0	0	0

As may be seen in table 4, 4 of the 5 deaths which occurred in the hospital were due to pneumothorax complications, while deaths after discharge were mainly caused by progressive tuberculosis.

The duration of the pneumothorax in relation to the results is presented in table 5. The number of patients is too small to show any correlation between

duration of treatment and results. The striking observation is that in most of the patients the pneumothorax was not maintained long enough. Only one patient had pneumothorax over the period of more than three years which is usually considered necessary.

Pneumothorax had to be abandoned for the following reasons: adhesions which could not be severed in 6 patients (one of these patients later had a successful thoracoplasty); development of pleural effusions (purulent in 2 cases) in 4 patients; bronchopleural fistulas in 2 patients; increase in cavity size in one patient (this patient later had a successful thoracoplasty). In only 2 patients was the pneumothorax abandoned as an elective procedure: in one after more than two years' duration, in one after more than four years' duration.

In table 6 may be seen the complications encountered in pneumothorax treatment.

TABLE 6

Complications of Pneumothorax Treatment in Middle-aged and Elderly Patients Treated with Pneumothorax

COMPLICATION	FATAL	NONFATAL	TOTAL
Increase in cavity size	—	1	1
Air embolism	1	—	1
Tension pneumothorax	1*	1	2
Unexpandable lung; respiratory failure	1	—	1
Bronchopleural fistula	2	—	2
Sterile pleural effusion	—	1	1
Tuberculous empyema	—	2	2
Mixed pyogenic bacterial empyema	1*	1	2
Total	6*	6	12

* Bronchopleural fistula was associated in one case with tension pneumothorax and in another with mixed empyema. Therefore, 2 patients are listed twice. The number of patients dying of pneumothorax complications was 4.

DISCUSSION

Although the number of patients in this group is quite small for comparison with studies dealing with young individuals, two striking differences are noted: first, the high incidence of complications, especially empyema; and second, the small number of patients in whom an effective pneumothorax space could be established and maintained for a sufficient period of time. The second difference is obviously related to, and partly a consequence of, the first.

The incidence of empyema is particularly high (4 of 17). Two of the patients with empyema were diabetics, but so were more than half of all the patients. The 2 patients with tuberculous empyema had poor collapse, while collapse was fairly satisfactory in those with empyema of nontuberculous origin. Endobronchial disease was apparently not an important factor in the high incidence of complications. All patients were bronchoscoped when endobronchial disease was suspected on clinical or roentgenographic grounds. Among the empyema pa-

tients, only one was bronchoscoped, but no abnormality was found. Streptomycin was not yet available at the time the patients in this study were given pneumothorax. It appears likely that at present, in conjunction with streptomycin administration, the number of complications would be less and the therapeutic results better.

Some of the patients in this group had disease of a type which is considered to be an indication for major surgery in young persons. However, surgical therapy was thought to be impossible or too dangerous in patients more than 50 years of age with complicating diabetes or cardiovascular impairment. Therefore, pneumothorax was tried in some cases with full awareness of its dangers, since no other therapy appeared to be available for an otherwise hopeless condition. For the same reason, there was sometimes more reluctance to give up a not completely satisfactory pneumothorax space than is usual with young patients. These circumstances probably account in part for the high incidence of complications, especially empyema.

In the higher age group, emphysema and heart disease are more frequent than in younger people. Cardiorespiratory insufficiency, therefore, occurs more often following pneumothorax induction. In one patient (not included in this group), the pneumothorax had to be discontinued immediately after successful induction because of severe dyspnea. One patient of the present group died from cardiorespiratory insufficiency.

SUMMARY

During the years 1939 to 1945, pneumothorax was induced in 20 patients, 50 to 64 years of age, with pulmonary tuberculosis. In 3 it had to be abandoned immediately; the remaining 17 patients form the basis of this study.

The disease was moderately advanced in 3 and far advanced in 14 patients; severe associated diseases were present in 11 patients.

In 7 of the 17 patients sputum "conversion" was achieved. In only 5 of the patients, however, could this result be attributed to pneumothorax treatment. Five patients were discharged with sputum containing tubercle bacilli, and 5 died at the hospital.

Frequently, pneumothorax treatment had to be discontinued because of inadequacy of the space or because of complications. The complications which developed were: increase in cavity size, air embolism, tension pneumothorax, unexpandable lung, bronchopleural fistula, sterile pleural effusion, tuberculous empyema, and mixed pyogenic bacterial empyema. It should be noted, however, that these patients were treated before effective chemotherapy was available.

The patients discharged as arrested or quiescent tended to maintain their status during the follow-up period.

It is particularly important to abandon an ineffective pneumothorax immediately in patients in this age group (50 to 64 years). In patients with good collapse and sputum "conversion," the long-term results appear to be as satisfactory as in younger individuals.

Addendum

After the completion of this paper, the following article appeared: Leech, E. L.: Problems presented by pulmonary tuberculosis in patients over fifty, Ann. Int. Med., 1950, *33*, 321. The writer concluded: "Collapse therapy can and should be employed in the treatment of the more aged patients whenever the indications outweigh the contraindications. Therapeutic successes may come when least expected".

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TUBERCULOSIS IN MEDICAL AND NURSING STUDENTS[1]

RICHARD C. BATES AND WINTHROP N. DAVEY

(Received for publication August 10, 1950)

It has been recognized for many years that students of nursing and medicine have a greater rate of "tuberculin conversion" and a higher incidence of clinical pulmonary tuberculosis than do students in other fields (1, 2, 3). To the literature on this subject the writers would like to add the results of ten years' observation of student nurses and three years' observation of medical students at the University of Michigan.

MATERIALS AND METHODS

Tuberculin skin testing of these groups is performed at six-month intervals: immediately following entrance or return to school in October, and again in April prior to the end of the school year. The material used is purified protein derivative (PPD) supplied by the Public Health Service through the Phipps Institute[2]. Two doses, 0.0001 mg. and 0.005 mg., are given intracutaneously.

Seventy-millimeter microfluorograms of the chest are taken on each student at the time of tuberculin testing and interpreted by members of the Department of Roentgenology of University Hospital. If abnormalities are noted, the findings are checked on 14 by 17 stereoscopic chest roentgenograms. In students who convert their tuberculin reaction to positive, 14 by 17 stereoscopic chest roentgenograms are obtained at three-month intervals for two years thereafter, or until graduation.

The tuberculin tests are examined at twenty-four and forty-eight hours. If less than 5 mm. of induration is present at forty-eight hours, the test is regarded as negative and the next stronger dilution is administered or the student dismissed, as is the case when the second dose has been used. If 5 mm. or more of induration are present at forty-eight hours, a seventy-two-hour reading is made. If less than 5 mm. of induration is present at that time, the tuberculin reaction is called negative; otherwise, it is positive.

Tuberculin skin tests are repeated at six-month intervals until the student develops more than 10 mm. of induration seventy-two hours following administration of the 0.0001 mg. dose of PPD. Microfluorograms, however, are obtained at least every six months on every student, regardless of the tuberculin reaction.

In the present report, *tuberculin conversion* is defined as sensitivity to a 0.0001 mg. quantity of PPD by a person not previously sensitive to that quantity. The state of *sensitivity* is considered to be present when intracutaneous induration, 5 mm. or more in diameter, is present both at forty-eight and at seventy-two hours following the injection.

Active pulmonary tuberculosis is considered to be present in any tuberculin-positive student who has roentgenographic evidence of a lesion in a lung which was not present on previous examinations and which changes in extent or character during observation and treatment, and is interpreted by the roentgenologists and phthisiologists as compatible with tuberculous infection. The recovery of tubercle bacilli from the patient is not included as a criterion for the diagnosis in this report since the goal is to detect every case before bacilli are demonstrable in the sputum.

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[1] From the Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan.

[2] The Henry Phipps Institute, Philadelphia, Pennsylvania.

RESULTS

In the figures (1–3) and in table 1 are shown the results of examinations of 1,247 student nurses and 735 medical students over the stated periods of time. Included are 20 cases of active pulmonary tuberculosis; all but 2 minimal in extent; all, without exception, occurring in students who were tuberculin negative

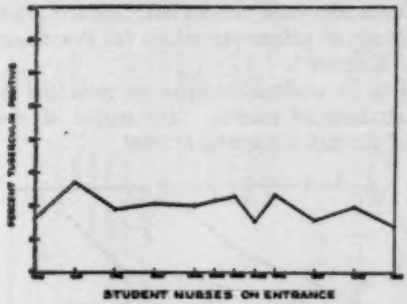

FIG. 1. Percentage of entering student nurses sensitive to 0.0001 mg. of PPD Total number of students ranged from 61 to 165.

In 1944 and 1945, classes were entered in the spring as well as in the fall and are indicated as "1944–B" and "1945-B".

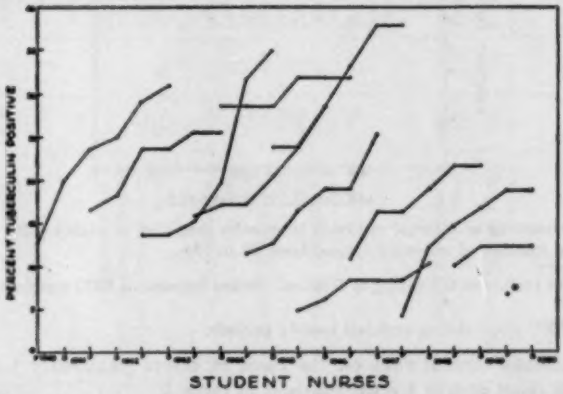

FIG. 2. Percentage of student nurses tuberculin sensitive at each testing period by classes. Total number of students ranged from 23 to 87.

* Results of testing in the spring of 1950 not plotted because of BCG vaccination of part of the class.

"S" and "F" mean spring and fall testing periods.

on entrance to school. These 20 cases represent all of the cases of pulmonary tuberculosis which appeared during the period of this study.

In figure 1 may be seen the incidence of tuberculin sensitivity in all students entering the School of Nursing of the University of Michigan from October 1940 through April 1950.

Figure 2 demonstrates the rates of tuberculin conversion in the 641 student nurses who either: (*1*) completed three years of training; (*2*) are still enrolled in school; or (*3*) left school because of active pulmonary tuberculosis. Since almost one-half of the students who enter nursing school do not graduate, the incidence of tuberculin sensitivity at entance to school for this group differs somewhat from that depicted in figure 1.

In figure 3 the data for medical students are presented in the same manner as in figure 2 for students of nursing. The period of observation extended from the fall of 1947 through the spring of 1950.

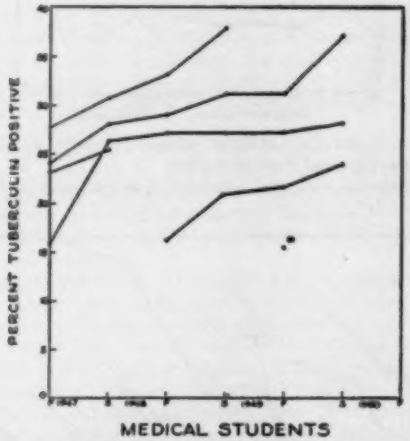

FIG. 3. Percentage of medical students tuberculin sensitive at each testing period, by classes. Total number of students ranged from 92 to 179.

* Results of testing in the spring of 1950 not plotted because of BCG vaccination of part of the class.

"S" and "F" mean spring and fall testing periods.

The significant clinical data on the cases of active pulmonary tuberculosis occurring in these groups are summarized in table 1.

DISCUSSION

It is unfortunate that each school carrying on a program of this type has used different criteria in analyzing its results. On the basis of the present experience, it is believed that more rigid definition of tuberculin "positivity" and "conversion" than that used in many reports is necessary if accurate studies are to be obtained. In this connection it should be pointed out that almost all of the stu-

TABLE 1

Clinical Data on Cases of Active Pulmonary Tuberculosis

CASE NUMBER	AGE	SEX	RACE	SCHOOL	SIZE OF LESION WHEN DETECTED	GREATEST SIZE OF LESION	MONTHS OF HOSPITALIZATION	RECOVERY OF TUBERCLE BACILLI	ADDITIONAL THERAPY	NUMBER OF RELAPSES TO DATE	DATE OF FIRST ROENTGENOGRAPHIC EVIDENCE OF TUBERCULOSIS	MONTHS BETWEEN DETECTION OF TUBERCULIN "CONVERSION" AND FIRST ROENTGENOGRAPHIC EVIDENCE OF TUBERCULOSIS
1	20	F	W	Nursing	Minimal with pleural effusion	Minimal	16	No	Three phrenic crushes	0	8/10/44	0
2	20	F	W	Nursing	Minimal	Minimal	11	No	None	0	9/15/44	12
3	19	F	W	Nursing	Moderately advanced Bilateral	Moderately advanced Bilateral	17	Yes	Three phrenic crushes	0	12/13/44	0
4	20	F	W	Nursing	Minimal	Minimal	10	No	None	0	3/30/45	0
5	21	F	W	Nursing	Minimal	Minimal	10	Yes	None	0	9/15/45	−6†
6	24	F	W	Nursing	Minimal	Minimal	19	Yes	Two phrenic crushes	0	10/ 6/45	0
7	21	F	W	Nursing	Minimal	Minimal	11	No	None	0	4/18/46	0
8	20	F	W	Nursing	Minimal	Minimal	10	No	None	0	5/19/46	1
9	18	F	W	Nursing	Minimal	Minimal	13	No	One phrenic crush	0	4/20/46	0
10	23	F	W	Nursing	Minimal	Minimal	10	No	None	0	1/ 9/46	3
11	21	F	W	Nursing	Minimal with adenopathy	Minimal	11	No	None	0	7/ 8/46	3
12	21	F	W	Nursing	Minimal with tuberculous bronchitis and adenopathy	Minimal	12	No	Streptomycin	0	1/13/47	−1
13	23	F	W	Nursing	Minimal	Minimal	12	Yes	None	0	11/20/47	1
14	22	F	W	Nursing	Moderately advanced with cavitation	Moderately advanced with cavitation	*	Yes	Three phrenic crushes, pneumothorax, pneumoperitoneum	0	10/30/47	5
15	29	M	W	Medical	Minimal	Minimal	*	Yes	One phrenic crush, pneumothorax	1‡	5/ 2/49	0
16	21	F	W	Nursing	Minimal	Minimal	11	No	None	0	6/17/49	3
17	28	M	N	Medical	Minimal with adenopathy	Minimal	*	Yes	Streptomycin with PAS	0	1/ 2/50	0
18	25	F	N	Medical	Minimal with adenopathy	Minimal	*	No	Streptomycin with PAS	0	1/30/50	0
19	26	F	W	Medical	Minimal with adenopathy	Minimal	*	Yes	Streptomycin with PAS	0	3/31/50	0
20	23	M	W	Medical	Minimal with bilateral pleural effusions	Minimal	*	No	None	0	5/27/50	−2

* Still hospitalized.
† Sputum positive for tubercle bacilli six months before tuberculin "conversion."
‡ Relapsed while under initial hospitalization.

dents with active disease became tuberculin positive within a few months of the appearance of a lesion in the lungs, and all were tuberculin negative on entrance to school. Thus, in these 20 cases at least, the accuracy of the evaluation has been verified. Enough is known about the tuberculin reaction at this time so that it should be possible for a suitable organization to recommend standards for testing student groups to facilitate comparison of results throughout the country.

Many reports in the literature have used "conversion" to 0.005 mg. PPD as a criterion for acquisition of tuberculous infection. As Furcolow and his associates (4) have shown, nonspecific reactions to this dose occur and this has been true in the writers' experience, particularly if readings were to be discontinued at the end of forty-eight hours. Fully one-fourth of the subjects who appeared to have "converted" to this dose were no longer sensitive to it at the next testing period six months later. As a consequence, it has not been possible to interpret results of testing to this dose.

Although it has never been proved that tuberculin sensitivity is directly related to resistance to tuberculous infection (5, 6), no case of active tuberculosis occurred in any of these students who were tuberculin positive on entrance to school. As a matter of fact, these patients with active tuberculosis were also, without exception, insensitive to the dose of 0.005 mg. on entrance as well.

Because of this and in spite of the fact that BCG vaccination, in the writers' experience, does not often create sensitivity to the 0.0001 mg. dose, the use of this agent was started in the fall of 1949 on new students. It was hoped that BCG-induced sensitivity to the larger dose might still provide sufficient protection against infection.

In the present study it has not been possible to show, as has been demonstrated elsewhere (7), that the incidence of tuberculin sensitivity is decreasing in succeeding classes of new students. In fact, as may be seen in figure 1, during the past ten years the incidence of positive tuberculin reactions among students entering the nursing school has been remarkably constant. Likewise, it has not been possible to find any one year in either school in which a particular hazard of tuberculous infection was represented.

The sharp decline of tuberculin sensitivity of succeeding classes of entering medical students is thought to represent the effects of older veterans beginning school in 1947 compared with the younger non-veterans entering at present. The higher rate of tuberculin sensitivity of medical students compared to that of nurses is similarly thought to reflect age differences rather than any increased exposure in the former group.

The testing interval of six months is apparently adequate, since only 2 of 20 tuberculous lesions were more than minimal when detected. This is in agreement with the Harvard workers who found six months to be the maximum allowable interval if cases are to be detected while still minimal (8).

Some surprise may be expressed that patients with even the least extensive minimal primary lesions and sputum negative for tubercle bacilli were treated

by sanatorium care, which meant strict confinement to bed until stabilization had been apparent for at least three months. The writers are in agreement with Muschenheim, Bunn, and Lansdown (9) that primary disease in this age group may often progress. It has been found that, in 60 per cent of the employees in this hospital with new, minimal tuberculous disease, the lesion progressed if untreated (10).

Although the observation interval has been short, the presence of only one relapse and no case of progression to more serious disease in the cases of the present report would appear to support these views.

SUMMARY

The results of tuberculin testing and roentgenographic examinations of the chest at six-month intervals on all students in nursing and medicine at the University of Michigan are reported. The data cover a ten-year period for student nurses and a three-year period for medical students.

No evidence of a decreasing incidence of tuberculin sensitivity in succeeding classes was found, nor could any one school year be shown to be associated with increased hazards of infection.

Twenty cases of active pulmonary tuberculosis were detected and all but 2 were minimal when first discovered. In no instance has the lesion progressed under observation to more serious disease, and the infection has relapsed in only one patient to date. All cases of active tuberculosis appeared in students who had been negative to 0.005 mg. of PPD on entrance to school.

It is suggested that programs of tuberculin testing in schools throughout the country be standardized so that results will be comparable.

SUMARIO

Tuberculosis en los Estudiantes de Medicina y de Enfermería

Esta exposición comprende los resultados de la comprobación con tuberculina y de los exámenes radiográficos del tórax a plazos de seis meses en todos los estudiantes de enfermería y de medicina de la Universidad de Michigan. Los datos abarcan un período de diez años para los de enfermería y tres años para los de medicina.

No se descubrieron signos de menor incidencia de sensibilidad a la tuberculina en las clases sucedientes, ni tampoco pudo observarse que ningún año escolar dado mostrara mayor peligro de infección.

En esta encuesta, descubriéronse 20 casos de tuberculosis pulmonar activa, cuyo análisis se presenta. Todos, menos 2 de ellos, eran mínimos al ser descubiertos por primera vez, ninguno se agravó mientras era mantenido en observación, y sólo uno ha recidivado hasta la fecha. Todos los casos activos ocurrieron en estudiantes negativos a 0.005 mg. de PPD a su ingreso en la escuela.

Convendría uniformizar las obras de comprobación con tuberculina en las facultades de medicina y otras a fin de obtener resultados comparables.

RESUME

Tuberculose chez les étudiants en médecine et chez les élèves infirmières

Les résultats des tests à la tuberculine et les radiographies du poumon pratiqués tous les six mois chez tous les étudiants en médecine et les élèves infirmières de l'Université du Michigan sont rapportés. Les observations couvrent une période de dix années pour les élèves infirmières et de trois ans pour les étudiants en médecine.

La preuve d'une diminution de l'incidence de la sensibilité à la tuberculine dans les classes qui se sont succédées n'a pu être obtenue; de même, aucune année scolaire n'a permis d'observer une susceptibilité plus grande à l'infection.

Dans cette enquête, 20 cas de tuberculose pulmonaire en évolution ont été découverts et l'analyse en est présentée. Tous, sauf deux d'entre eux, étaient des cas légers au moment où ils ont été diagnostiqués, aucun n'a subi d'aggravation; à ce jour, une seule rechute a été observée.

Tous les cas en évolution se sont développés chez les sujets ayant présenté une réaction négative à 0,005 mg. de PPD au moment de leur entrée à l'école.

La normalisation des programmes relatifs aux tests à la tuberculine, dans le pays tout entier, est suggérée de manière à obtenir des résultats comparables.

Acknowledgment

Grateful acknowledgement is made to Drs. John B. Barnwell and Daniel Jenkins who initiated these studies; to Dr. Robert S. MacIntyre of the Department of Roentgenology who has reviewed most of the films; and to Dr. Gerald Drake and many others who have read the more than 14,000 tuberculin tests entailed in these surveys.

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THE THERAPEUTIC EFFECT ON EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS OF 4-ACETYLAMINOBENZAL THIOSEMICARBAZONE (TIBIONE) IN COMBINATION WITH DIHYDROSTREPTOMYCIN AS COMPARED WITH THE EFFECT OF PARA-AMINOSALICYLIC ACID IN COMBINATION WITH DIHYDROSTREPTOMYCIN[1]

DAVID M. SPAIN AND WILLIAM G. CHILDRESS

(Received for publication August 30, 1950)

INTRODUCTION

Domagk (1), Karlson, Gainer, and Feldman (2), Donovick and Bernstein (3), and Spain, Childress, and Fishler (4) have demonstrated the effectiveness of the thiosemicarbazones in inhibiting experimental tuberculosis in animals. Karlson and associates (2) have reported that 4-acetylaminobenzaldehyde thiosemicarbazone combined with a subeffective dose of streptomycin (2 mg.) was equivalent to the effective dose (6 mg.) of streptomycin in controlling experimental tuberculosis in guinea pigs. The purpose of the present study was to compare the antituberculous activity of 4-acetylaminobenzal thiosemicarbazone (Tibione)[2] combined with a subeffective dose of dihydrostreptomycin with the effectiveness of para-aminosalicylic acid combined with a similar dose of dihydrostreptomycin on experimental tuberculosis in guinea pigs.

MATERIALS AND METHODS

Seventy-five female guinea pigs weighing 300 to 325 gm. were observed under controlled conditions to ensure that they were healthy, were then tested with tuberculin, and divided into equivalent groups of 15 each. The animals were fed on Purina chow supplemented with oats and daily greens. No water was given.

A previously grown culture of H37Rv[3] was weighed and emulsified under aseptic conditions so that 0.2 mg. was the infecting dose per animal. The injections were made subcutaneously over the sternum.

Twenty-eight days post infection, 5 guinea pigs (pretreatment controls *Group I*) were sacrificed and autopsied. The findings are tabulated in figure 2.

Two days later treatment for each group was started as follows:

Group I. Pretreatment controls

Group II. Ten guinea pigs which received no treatment during the course of the entire experiment

Group III. Fifteen guinea pigs which received 50 mg. plus or minus of 4-acetylaminobenzal thiosemicarbazone (Tibione) daily in their food

Group IV. Fifteen guinea pigs injected subcutaneously with 2 mg. of dihydrostreptomycin hydrochloride each day

[1] From the Division of Tuberculosis and the Division of Pathology, Grasslands Hospital and the Department of Laboratories and Research of Westchester County, Valhalla, New York.

[2] The Tibione used in this study was supplied by Schenley Laboratories, Inc., New York N. Y.

[3] Obtained from Mr. W. Steenken, Jr., National Culture Bank, Trudeau Foundation, Saranac Lake, New York.

FIG. 1. Schematic representation showing key of symbols indicating extent of tuberculous lesions seen at necropsy (modified by authors from Feldman, W. H., and Hinshaw, H. C.: Am. Rev. Tuberc., 1945, *51*, 582).

Key:

1. Lesion over sternum at site of inoculation
1a. Ulcer at site of inoculation
2. Involvement of axillary lymph nodes
3. Involvement of mediastinal lymph nodes
4. Involvement of lungs
5. Nodular tuberculosis of spleen
6. Miliary tubercles in lung
7. Animal died days
8. Small lesion in either lung, liver, or spleen
9. Large lesion in lung, liver, or spleen

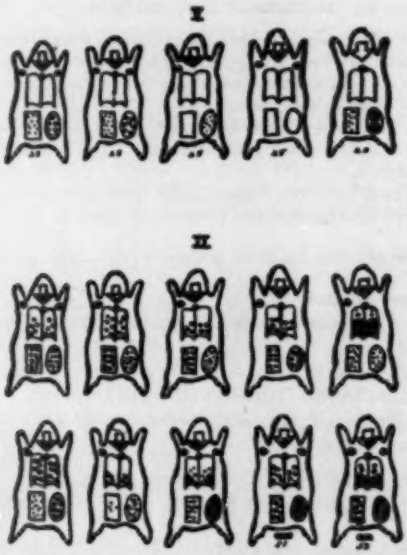

FIG. 2. Schematic representation of degree of involvement of (*Group I*) pretreatment controls and *Group II* controls.

Group V. Fifteen guinea pigs which received 50 mg. plus or minus Tibione in their food and were also injected subcutaneously with 2 mg. of dihydrostreptomycin hydrochloride each day

Group VI. Fifteen guinea pigs which received 100 mg. plus or minus PAS in their food and were also injected with 2 mg. of dihydrostreptomycin hydrochloride each day.

In each group listed above, the medication was weighed into known amounts of food and the amount of food remaining was checked daily. The medication in the diet and the dihydrostreptomycin injections were continued for thirty consecutive days. Prior to sacrifice each animal was weighed. After sixty days of infection and thirty days of treatment all of the animals were sacrificed. Com-

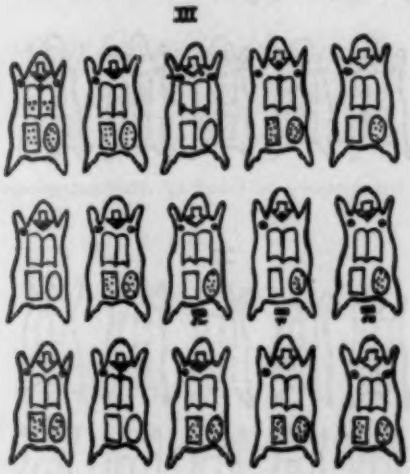

FIG. 3. Schematic representation of *Group III* Tibione (50 mg.)-treated animals.

plete autopsies were performed with particular attention to the site of inoculation, axillary and mediastinal lymph nodes, spleen, liver, and lungs. Gross and microscopic observations were recorded. These recordings were made, with some modification, according to the scheme of Feldman and Hinshaw (5).

RESULTS

The comparative findings among the six groups of animals are presented in figures 2, 3, 4, 5, and 6. The key to these figures is presented in figure 1.

Observations of the Site of Infection

All of the animals had ulcers at the infection site before treatment was started, with the exception of one guinea pig in the pretreatment control group. The

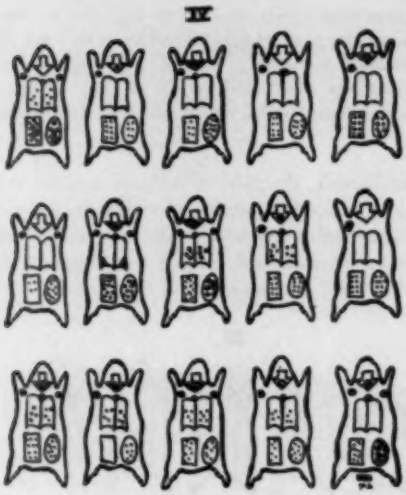

FIG. 4. Schematic representation of *Group IV* dihydrostreptomycin (2 mg.)-treated animals.

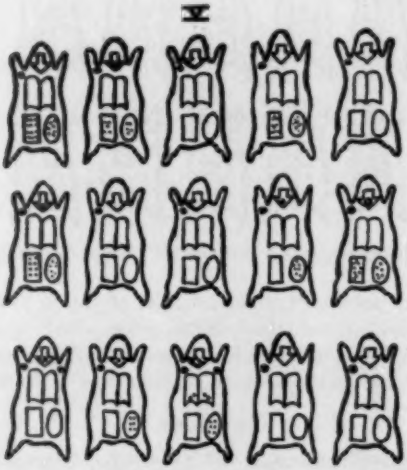

FIG. 5. Schematic representation of *Group V* Tibione (50 mg.)-and dihydrostreptomycin (2 mg.)-treated animals.

ulcers in the guinea pigs which received both Tibione and dihydrostreptomycin (*Group V*) showed evidence of healing most rapidly. Many of the ulcers were completely healed at the time of sacrifice. Those that were not healed in this

group, however, were markedly reduced in size and showed only slight evidence of residual infection. In the guinea pigs which received PAS combined with dihydrostreptomycin (*Group VI*), only a few ulcers were completely healed and the remaining ulcers showed little evidence of healing as compared with the animals in *Group V*.

Observations on the Extent of Tuberculous Involvement

The extent of involvement was graded on the basis of degree of ulceration and the healing of the inoculation site, the size and degree of abscess formation of the axillary and mediastinal lymph nodes involved, and the extent of involvement and healing in such organs as the liver, lung, and spleen (figure 1). The

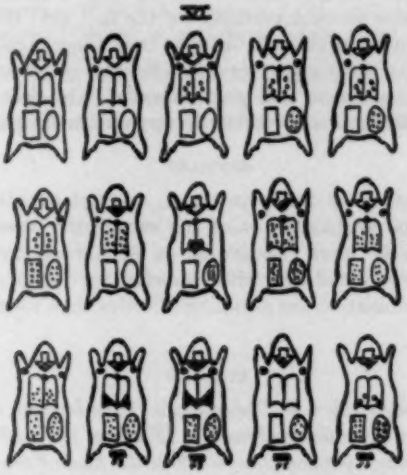

FIG. 6. Schematic representation of *Group VI* PAS (100 mg.)-and dihydrostreptomycin (2 mg.)-treated animals.

control animals (*Group II*, figure 2) exhibited the most marked involvement of all the organs studied. Microscopically, there was the usual fibrous tissue response, necrosis, and tubercle formation with no significant evidence of resolution or healing. The Tibione-treated animals (*Group III*, figure 3) showed much less involvement and there was definite evidence of healing and resolution. This was true to a lesser extent of that group of animals which received the subeffective dose of dihydrostreptomycin (*Group IV*, figure 4). The animals which received both Tibione and dihydrostreptomycin (*Group V*, figure 5) showed the most marked evidence of healing and resolution with the least involvement of the lungs, liver, and spleen. Only one animal in this group (*Group V*) revealed lung involvement, and the only evidence of tuberculous infection in 7 of the animals was seen in the residua of the infection site and in the axillary lymph nodes.

Splenic and hepatic involvement in the remaining animals in this group was minimal. The guinea pigs which received both PAS and dihydrostreptomycin showed considerably more involvement than those in *Group V*. As a matter of fact, very little difference in the extent of tuberculous involvement could be noted between this group and those animals which received only the subeffective dose of dihydrostreptomycin.

Observations on Weight

All groups of animals with the exception of the PAS-dihydrostreptomycin group gained on the average of 125 gm. per animal during the course of the experiment. The guinea pigs in *Group VI* gained on the average of 35 gm. less per animal than the other groups. This may have been a manifestation of PAS toxicity and may also account partially for the fact that the results obtained in this group were not significantly different from those obtained with the subeffective dose of dihydrostreptomycin alone. Several of the animals died during the course of the experiment, and were autopsied. The date of death and the findings in these animals are recorded in the appropriate figures.

SUMMARY

Under the conditions of this experiment, 4-acetylaminobenzal thiosemicarbazone (Tibione) in combination with the subeffective dose of dihydrostreptomycin proved to be more effective as an antituberculous agent in guinea pigs than the combination of PAS with a subeffective dose of dihydrostreptomycin. The former combination was also more effective than when Tibione was used alone.

SUMARIO

El Efecto Terapéutico sobre la Tuberculosis Experimental del Cobayo, de la Tiosemicarbazona 4-Acetilaminobenzálica (Tibiona) en Combinación con la Dihidroestreptomicina, Comparado con el Efecto del Acido Para-Aminosalicílico en Combinación con la Dihidroestreptomicina

En las condiciones de este experimento, la tiosemicarbazona 4-acetilaminobenzálica (Tibiona) combinada con la dosis subefectiva de dihidroestreptomicina se mostró más eficaz como agente antituberculoso en los cobayos que la combinación de PAS con una dosis subefectiva de dihidroestreptomicina. La primera combinación también resultó más eficaz que la Tibiona sola.

RESUME

Effet thérapeutique du 4-acétylaminobenzal thiosemicarbazone (Tibione) associé à la dihydrostreptomycine comparé à l'action de l'acide para-amino-salicylique associé à la dihydrostreptomycine dans la tuberculose expérimentale du cobaye

Dans les conditions de l'expérimentation, le 4-acétylaminobenzal thiosémicarbazone (Tibione) associé à une dose subthérapeutique de dihydrostreptomycine s'est montré plus efficace comme agent antituberculeux, chez le cobaye,

que la combinaison du traitement avec le PAS associé à une dose subthérapeutique de dihydrostreptomycine. Cette combinaison s'est également montrée plus efficace que lorsque le Tibione était administré seul.

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TUBERCLE BACILLI IN BONE MARROW[1,2,3]

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INTRODUCTION

Ever since the discovery of the tubercle bacillus in 1882, the problem of tuberculous bacillemia has been of interest to the students of tuberculosis.

Wilson (1), in his monograph, *Tuberculous Bacillaemia*, reviewed the work done from 1884 to 1933. He summarized the findings of other authors, beginning with Weichselbaum who in 1884 was the first to demonstrate "the presence of acid-fast bacilli in the blood of tuberculous patients." This study was done on 3 cases of miliary tuberculosis. In each case, a small number of bacilli were found in the stained slides of post-mortem blood. Other investigators used blood obtained from the living, either from the finger tip or by venipuncture. The processing was done either on direct smear, culture, or guinea pig inoculation. The results reported by the numerous workers varied all the way from 0 to 100 per cent. Wilson critically investigated Lōwenstein's work, which had caused quite a furor in the medical profession in the late nineteen twenties and early thirties. Lōwenstein, due to his prominence as an eminent bacteriologist, had astounded all by apparently culturing from the blood tubercle bacilli, not only in a great percentage of cases in all forms of clinical tuberculosis, but also in a large number of disease entities which had been thought to have no relation to a tuberculous infection. These ranged from rheumatism to diseases of the central nervous system such as multiple sclerosis. Wilson fully demonstrated the numerous fallacies in the method employed by Lōwenstein and his co-workers.

The literature is quite meager concerning the use and value of the bone marrow aspiration as an aid in establishing the diagnosis of hematogenous dissemination. Leitner (2), in his series of 54 cases of hematogenous tuberculosis, obtained only one positive culture from the aspirated sternal bone marrow material.

Schleicher (3) quoted the work of Stahel who observed tubercle formations in sections made from the bone marrow of a terminal case of miliary tuberculosis. Schleicher demonstrated, in his 8 cases, miliary tubercle formations in the so-called aspirated "bone marrow units."

Peterson and Canfield (4), using a similar approach, presented a striking comparison of cases in which the problem of "miliary tuberculosis versus typhoid

[1] From O'Reilly Veterans Administration Hospital, Springfield, Missouri.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

[3] Presented at the meeting of the Mississippi Valley Trudeau Society, Columbus, Ohio, on September 22, 1950.

fever" was discussed. They emphasized the value of histologic examination of aspirated bone marrow units as an aid in the differential diagnosis.

The present investigation was prompted by the observation that in a number of tuberculous cases examined post-mortem evidence of miliary disease was found, although its presence had not been detected roentgenographically during life. It was apparent, therefore, that a hemic dissemination had occurred in those patients some time before death.

PLAN OF INVESTIGATION

The present report is based on the findings in 20 patients from whom bone marrow material was aspirated. Examination of the processed stained smears and the entire procedure as outlined below can be accomplished in a matter of hours. It is believed that the diagnostic morphologic characteristics of the stained organism in the bone marrow material are as reliable as those made on a processed specimen of sputum. The pitfalls and dangers in the use of these techniques as set forth by Wilson (1) were taken into consideration.

The cases were selected from patients who presented the following criteria:

1. Patients with far advanced active pulmonary tuberculosis who exhibited toxemia as manifested by pyrexia and malaise, with or without signs of blood dyscrasia.
2. Patients whose chest roentgenograms revealed a miliary-like seeding, but whose sputum or other discharges were negative for tubercle bacilli.
3. Patients whose diagnosis on admission had been fever of unknown etiology of several weeks' duration and in whom the previous laboratory studies had been unrevealing. This group also included patients with clinical signs of non-purulent meningitis.
4. Several patients who had far advanced active pulmonary tuberculosis, but were afebrile.

Technique and Procedure (5, 6, 7)

An area, 3 to 5 cm., behind the anterior superior spine of the ilium was cleansed. The skin, soft tissue, and periosteum were well infiltrated with 1 to 2 per cent procaine hydrochloride solution. The bone marrow needle, with the stylet in place, was gently inserted through the skin down to the bone, and then slightly more pressure was applied at the same time that a rotary motion was used. A sensation of "give" indicated that the tip of the needle was in the marrow. The stylet was then removed, a 20-cubic centimeter syringe was attached, and 3 to 5 cc. of bone marrow material were aspirated. The specimen was placed in a sterile test tube containing 3 cc. of 10 per cent sodium citrate and 1 cc. of 23 per cent trisodium phosphate.

The mixture was put into an Erlenmeyer flask and mixed with 100 cc. of 1 per cent acetic acid. The mixture was gently rotated for approximately a minute and allowed to stand at room temperature for thirty minutes, when it was transferred to centrifuge tubes and centrifuged at 1,500 r.p.m. for one hour. The supernatant fluid was carefully decanted and the sediments were combined and treated with 10 cc. of Hank's solution.[4] The mixture was incubated at 37° C. for one-half hour, after which it was neutralized with 10 per cent hydrochloric acid and 10 per cent sodium hydroxide, using 0.4 per cent brown cresol purple in 95

[4] Hank's solution: 4.0 gm. NaOH, 1.0 gm. K Alum, 100 cc. distilled water.

per cent alcohol as an indicator. The neutralized specimen was centrifuged at 2,500 r.p.m. for thirty minutes, the supernatant fluid decanted, and the sediment resuspended in 10 cc. of sterile normal saline. The suspension was centrifuged at 2,500 r.p.m. for thirty minutes, the supernatant fluid decanted, and the sediment resuspended in 10 cc. of sterile normal saline. This was centrifuged again at 2,500 r.p.m. for thirty minutes. The supernatant fluid was decanted and the remaining portion was used to make smears, as inoculum into guinea pigs, or as prepared media such as Löwenstein, Petragnani, Petroff, or Dubos. Where malachite green was used in the media, the quantity of the dye did not exceed 1.3 per cent. In the preparation of smears, a drop of the sediment was smeared into a drop of Mayer's egg albumin. The smear was allowed to dry, fixed by heat, and was stained either by the Ziehl-Neelsen or the Kinyoun method. The stained smear was examined for one-half to one hour for acid-fast bacilli.

In the preparation of solutions, the water must be glass distilled and examined for acid-fast contaminants. All glassware must be sterile.

The iliac crest bone marrow aspiration is a simple, innocuous, and relatively painless procedure, as Rubinstein (8) has indicated. There is a slight discomfort during the actual aspiration. The writers are convinced that it is the site of choice for bone marrow aspirations in patients with pulmonary tuberculosis.

OBSERVATIONS

The results of the bone marrow studies on 20 patients are given in table 1. To date only one marrow aspiration has been performed per patient with the exception of patient C. A. S. (table 1), on whom marrow study was negative during life; yet several weeks later examination of post-mortem marrow smears revealed numerous tubercle bacilli. It has been possible to demonstrate the presence of acid-fast bacilli on direct examination in 14 of the 20 patients, and five of the cultures seeded with the processed aspirated bone marrow material were positive for *M. tuberculosis*.

The column SM-PAS in table 1 refers to the length of time prior to the bone marrow aspiration during which each patient received streptomycin and para-aminosalicylic acid.

The majority of the 20 patients studied had far advanced active pulmonary tuberculosis of the type usually seen in any tuberculosis hospital. However, 5 patients of this group are worthy of more detailed case reports.

Case Reports

J. G. R., a 53-year-old white married farmer, was admitted to the medical service on October 14, 1949 with a diagnosis of fever of unknown etiology of two weeks' duration. He also had general malaise, occasional headache, anorexia, nausea, and some vomiting. His past history was noncontributory, except for a vague story of suspected pulmonary tuberculosis some twenty years previously.

On admission, physical examination revealed an acutely ill white male whose oral temperature was 102° F. The remainder of the physical examination, the routine laboratory tests, and various serologic studies were noncontributory. The chest roentgenogram was negative except for discrete, multiple, calcific deposits scattered throughout both lung fields.

The patient's elevated temperature persisted in spite of penicillin, aureomycin, and venoclysis. Forty-eight hours after admission, the patient complained of severe retrobulbar and occipital headache. The sensorium appeared clouded, and nuchal rigidity was apparent. Examination of the cerebrospinal fluid on October 16, 1949 revealed clear fluid under increased pressure, with a total leukocyte count of 145 cells per cu. mm. of which 95 per cent

TABLE 1

Status of Tuberculosis in Patients Whose Bone Marrow Was Aspirated

PATIENT	AGE	RACE	SEX	DURATION PRESENT ILLNESS	DIAGNOSIS	ROENTGENOGRAPHIC FINDINGS	TEMPERATURE	RBC	WBC	SEDIMENTATION RATE	ACID-FAST BACILLI IN SPUTUM	MICROSCOPIC EXAMINATION OF ASPIRATE	SM-PAS THERAPY BEFORE ASPIRATION	PRESENT STATUS
J. F.	22	N	M	6 months	FA* Pul.† TB	Pneumonic	98.6°F.	5.4	9.1	28	Positive	Positive	8 weeks	Living and improved
E. F.	27	W	M	1 year	FA Pul. TB	Cavitary	101°F.	4.8	14.5	34	Positive	Positive	None	Living and worse
E. C. F.	57	W	M	10 years	FA Pul. TB, tuberculous meningitis	Cavitary	100°F.	4.8	24.0	25	Positive	Positive	8 weeks	Died; autopsy
‡E. W.	57	W	M	1 year	FA Pul. TB, BPC§ fistula	Pneumonic	100°F.	5.4	14.7	41	Positive	Positive	42 days	Died; no autopsy
‡A. V. W.	60	W	M	6 months	MA‖ Pul. TB	Productive	10 °F.	3.5	3.8	13	Positive	Positive	None	Living and improved
‡J. E. K.	26	N	M	1 year	FA Pul. TB	Exudative	98.6°F.	4.8	9.4	34	Positive	Positive	90 days	Living and improved
E. L. S.	32	W	M	6 months	FA Pul. TB	Exudative	103°F.	1.7	0.725	28	Positive	Positive	30 days	Died; no autopsy
‡J. G. R.	53	W	M	3 weeks	FUO¶	Scattered calcific deposit	102°F.	4.6	7.3	31	Negative	Positive	None	Living and improved
S. N. M.	25	N	M	6 years	FA Pul. TB	Cavitary	98.6°F.	4.5	16.1	18	Positive	Positive	90 days	Living and improved
L. A. C.	27	W	M	7 years	FA Pul. TB, osteomyelitis	Cavitary	98.0°F.	4.5	19.8	34	Positive	Negative	7 days	Living and improved
W. J. M.	37	N	M	5 years	FA Pul. TB	Cavitary	103°F.	5.1	7.3	41	Positive	Positive	None	Living and improved
P. C.	39	W	M	2 years	FA Pul. TB, syphilis	Cavitary	102°F.	4.0	14.6	35	Positive	Negative	2 weeks	Died; no autopsy
W. D.	41	N	M	4 years	FA Pul. TB	Exudative	98.6°F.	4.2	13.5	32	Positive	Negative	90 days	Living and improved
E. C. G.	55	W	M	11 years	FA Pul. TB	Cavitary	102°F.	4.7	18.9	35	Positive	Negative	90 days	Died; no autopsy
‡C. O.	60	W	M	9 years	FA Pul. TB, miliary Pul. TB	Miliary	103°F.	4.4	4.6	31	Positive	Positive	2 weeks	Living and improved
C. A. S.	34	W	M	7 years	FA Pul. TB	Cavitary	101°F.	3.9	17.3	34	Positive	Negative Positive at autopsy	None	Died; autopsy
E. B.	34	W	M	7 years	FA Pul. TB	Cavitary	100°F.	4.2	9.5	32	Positive	Negative	120 days	Died; autopsy
G. C. F.	41	W	M	1 year	FA Pul. TB	Pneumonic	101°F.	4.0	21.6	20	Positive	Negative	42 days	Died; no autopsy
W. F.	25	N	M	3 years	FA Pul. TB	Cavitary	104°F.	4.0	13.1	25	Positive	Positive	90 days	Living and improved
**J. W.	70	W	M	13 years	FA Pul. TB	Cavitary	102°F.	4.6	22.4	38	Negative	Positive	None	Living and improved

* FA—far advanced.

† Pul.—pulmonary.

‡ The cultures of aspirated bone marrow material positive for *M. tuberculosis*.

§ Bronchopleurocutaneous.

‖ MA—moderately advanced.

¶ FUO—fever of unknown origin.

** Cultures of concentrated sputum positive for *M. tuberculosis* eight weeks after bone marrow biopsy report.

were lymphocytes. The chloride and total protein concentrations of the fluid were within normal limits except for a trace of globulin. Smears were negative for acid-fast bacilli and other organisms. Likewise, cultures for aerobic and anaerobic organisms were reported as negative. The fluid was also inoculated into a guinea pig and subsequently was reported as negative.

Bone marrow aspiration: On October 19, 1949 bone marrow aspiration was done and the processed smear revealed acid-fast bacilli. Later the material was positive for *M. tuberculosis* on culture.

A diagnosis of early, active tuberculous meningitis was thus established, and the patient was given streptomycin and para-aminosalicylic acid according to the meningeal regimen of the Veterans Administration protocol. He received no streptomycin intrathecally. The temperature gradually subsided to normal within a week and his sensorium cleared rapidly. Repeated examinations of the cerebrospinal fluid showed a drop in total leukocyte cells within a month to 23 per cu. mm.; and in six weeks, after institution of therapy, to 9 cells per cu. mm. Fifteen months after the acute onset of his illness, the patient is doing exceedingly well except for a slight ataxia, and is fully ambulatory.

E. L. S., a 32-year-old white married male, had been employed as a lead and zinc miner intermittently for some nine years. The onset of his illness occurred in May 1949 with "flu-like" symptoms. He was then hospitalized at another Veterans Administration hospital where a diagnosis of active pulmonary tuberculosis was made on the basis of "positive" sputum and interpretation of his roentgenograms. He also had a profound anemia for which he received numerous transfusions. He was given 1 gm. of streptomycin daily for approximately thirty days until he left against medical advice.

On admission to this hospital on November 3, 1949, he had a good deal of cough and expectoration and was very dyspneic. The physical examination revealed a markedly pale, acutely ill white male whose rectal temperature was 102° F. The lungs on auscultation revealed numerous coarse rales throughout. The heart sounds were of poor quality, and the rate was 140 per minute. The lower extremities and dependent portions of the body were markedly edematous. A chest film revealed extensive mottled densities throughout both lungs. In the right mid-lung field, the infiltrations appeared confluent and pneumonic. Blood counts on admission showed: erythrocytes, 1,700,000 per cu mm., total leukocytes, 725 per cu. mm.; and a hemoglobin concentration of 37 per cent. The platelet count was too low to evaluate, but there was no evidence of agranulocytosis. The total blood protein was 5.7 gm. per 100 cc. with an albumin-globulin ratio of 0.43. The urinalysis revealed numerous hyaline and granular casts with one plus albumin.

Bone marrow aspiration: On November 4, 1949 a processed smear of the aspirated bone marrow revealed acid-fast bacilli. In spite of transfusions, the patient died on November 7, 1949, and an autopsy could not be obtained. The final diagnosis was far advanced pulmonary tuberculosis with some silicotic components, panmyelophthsis, and probable cor pulmonale.

E. W., a 57-year-old white, married, former warehouse worker, was admitted to another Veterans Administration hospital in August 1948, where he had a left pneumonectomy performed for a transitional cell carcinoma. He soon developed an empyema which required frequent aspirations and subsequently developed a bronchopleurocutaneous fistula. In December 1948, a total thoracoplasty and an unroofing of the parietal pleura was done in an attempt to obliterate the pleural cavity. The histologic examination of the resected pleura revealed caseous tubercle formations. He was then given a 42-day course of streptomycin, 1 gm. daily, but the fistula failed to heal.

On transfer to this hospital on March 18, 1949 his sputum was found to contain tubercle bacilli. The chest film revealed a deformity on the left, due to a total thoracoplasty; and on the right, no abnormal densities. He was afebrile, and the remainder of the laboratory study was noncontributory. During the next few months he did fairly well except for a persistent purulent discharge from his fistula which contained tubercle bacilli. In July 1949,

after due observation, it was decided that this patient would require further surgery. Before surgery, however, a review of the microscopic sections of the excised left lung revealed, not only a transitional cell carcinoma, but also active tuberculosis.

On July 25, 1949 the patient had a chill with a rise in temperature to 103° F., and he became dyspneic. A chest film compared with the previous films showed a pneumonic "spread" to the right base. Streptomycin, 1 gm. daily, was instituted and continued for 120 days. His elevated temperature gradually subsided over a period of several weeks.

Bone marrow aspiration: On August 5, 1949 a smear of the processed aspirated bone marrow material contained acid-fast bacilli which were proved by culture to be tubercle bacilli. The patient's dyspnea continued and was thought to be due, in part, to cor pulmonale. Further serial chest roentgenograms revealed a progression of the disease in spite of streptomycin. He died on January 30, 1950, and permission for an autopsy was not granted.

A. V. W., a 51-year-old white married male, was transferred to the tuberculosis service from another Veterans Administration hospital on August 9, 1949 with a diagnosis of moderately advanced, active, pulmonary tuberculosis and Laennec's cirrhosis. The onset of his disease was in May 1949, at which time he was hospitalized, with vague abdominal pains, diarrhea, loss of approximately eleven pounds, and enlargement of his abdomen. Both sputum and stools were positive for tubercle bacilli. He ran a febrile course.

On admission to this hospital, the patient appeared acutely ill with temperature elevated to 101°F. Rales were audible in both mid-lung fields posteriorly. A fluid percussion wave was elicited over the abdomen. A chest roentgenogram revealed bilateral mid-lung productive infiltration. Soon after admission, an abdominal paracentesis was done and 3,300 cc. of clear, straw-colored fluid were withdrawn. The fluid was negative on smear and culture for tubercle bacilli. The patient gradually improved and during the next few months his elevated temperature subsided. In early October 1949, gastrointestinal roentgenographic studies revealed hypermotility and deformity of the cecum suggestive of tuberculous enterocolitis. On October 21, 1949, the patient had a chill with a sudden rise of temperature to 103°F. A chest roentgenogram on October 25, 1949 showed stationary lesions.

Bone marrow aspiration: On October 24, 1949, bone marrow aspiration revealed acid-fast bacilli on smear and the culture was subsequently positive for *M. tuberculosis*. The patient was given a 90-day course of streptomycin, 1 gm. daily. The elevated temperature rapidly subsided and the patient improved during the next few months. During the latter part of December 1949 and early January 1950, he complained of pain at the base of his tongue. On January 10, 1950, a small nodule at the right base of his tongue was biopsied and was reported as a squamous cell carcinoma. He was referred to a Veterans Administration tumor center where, on March 4, 1950, a radical neck resection and implantation of radon seeds were performed. He was then readmitted to this hospital on April 17, 1950. A chest film showed no change and his sputum was still positive for tubercle bacilli. On further examination, a beading and nodulation of the left epididymis was palpable. The patient stated that it had appeared a week prior to his last admission. It was tentatively diagnosed as tuberculous and on April 20, 1950 he was started on a 60-day re-treatment course of streptomycin and PAS. The right epididymis became involved in a similar process within a week. On May 24, 1950, a bilateral epididymectomy was performed, and the incisions healed by primary intention. On histologic examination, both epididymides revealed active tuberculosis. At present, the patient is on a 120-day course of PAS. He is doing well, with a constant weight gain, and has been afebrile for the past three months. There are no abdominal complaints and the findings are negative on examination. His serial roentgenograms reveal bilateral regression of the lesions and his sputum has been negative for tubercle bacilli on smear and culture since May 1950.

C. O., a 70-year-old married white male, was transferred to this hospital on July 19, 1949 from another Veterans Administration hospital, with a diagnosis of far advanced active pulmonary tuberculosis. In 1940 he had been hospitalized at a Veterans Administration

hospital for a minor condition. A chest roentgenogram then revealed bilateral upper lobe fibrocalcific infiltrations, heaviest on the right. The sputum was negative for tubercle bacilli. Subsequently during the next nine years he was in and out of that hospital and was last admitted there in the spring of 1949 with hematuria. His chest roentgenogram at that time showed a questionable cavity in the right infraclavicular region. In early July 1949, the patient developed intermittent high fever, and another chest roentgenogram revealed a disseminated miliary process throughout both lung fields.

On admission to this hospital he appeared acutely ill, with a rectal temperature of 104°F. He was disoriented but had no nuchal rigidity. Sputum was positive for tubercle bacilli and a chest roentgenogram showed no change in the miliary process. He was given streptomycin, which was continued for 120 days. Examination of the cerebrospinal fluid was normal. A serologic test for syphilis (Wassermann), however, which had previously been negative, was reported positive and remained so on repeated examinations until December 1949, when it reverted to negative. On July 21, 1949, one of the many urine specimens examined contained tubercle bacilli on inoculation into a guinea pig.

Bone marrow aspiration: Bone marrow aspiration on August 1, 1949 revealed acid-fast bacilli on smear and the culture was subsequently positive for *M. tuberculosis*. The patient improved rapidly on streptomycin therapy and by September 1949 his chest roentgenogram revealed a clearing of the miliary dissemination. He gained weight, but his sputum remained positive for tubercle bacilli during his stay in the hospital. On January 13, 1950 he left the hospital against medical advice and returned to his home. He was last heard from through his fellow patients and is apparently doing well.

DISCUSSION

Before the chemotherapeutic era in the treatment of tuberculosis, the diagnosis of tuberculous bacillemia had hardly any practical value and was merely of didactic or speculative interest. With the advent of the epochal work of Schatz and Waksman (9) on streptomycin and Lehmann's study (10) on para-aminosalicylic acid, it has become of paramount importance that the diagnosis of hematogenous tuberculosis and tuberculous meningitis be established as early as possible. J. A. Myers (11), in an editorial several years ago, stressed the value of early diagnosis of generalized hematogenous tuberculosis. Interestingly, this was written before the advent of streptomycin and para-aminosalicylic acid. McDermott and his associates (12), in commenting on the use of streptomycin in tuberculous meningitis, state that, although the drug has an "effect upon the course of the meningeal infection, the central nervous system presumably had been damaged, before treatment, to an extent which precluded ultimate recovery." Once the pathologic process of fibrin deposition and its organization has started, the value of present-day antimicrobial agents, even with the use of streptokinase or other lytic enzymes, is greatly diminished. Likewise, in miliary tuberculosis it is essential that the specific therapy, to be of any value, be initiated before extensive caseation and conglomeration has occurred.

The value of early diagnosis of tuberculous bacillemia and its most deadly complication is well exemplified in the patient J. A. R. The findings, with the report of the first spinal tap, which were at most only slightly suggestive of a tuberculous meningitis, were a leukocytosis with a lymphocytosis of the spinal fluid. It is believed that had the usual practice been followed, i.e., of waiting until more definite corroboration of tuberculous meningitis was at hand, this patient probably would not have shown the improvement he did.

Patient C. O., who was admitted with early miliary pulmonary tuberculosis as a manifestation of his tuberculous bacillemia, showed the value of beginning specific therapy before extensive caseation and conglomeration had occurred. He made a nice recovery in spite of his advanced age. It can be safely stated that the seeding with tubercle bacilli occurred, not only in the lesser circulation, but also in the greater as evidenced by finding the organisms in the bone marrow.

Patient A. V. W. presented on admission an enlargement of his abdomen due to peritoneal fluid and was found to have advanced Laennec's cirrhosis in addition to moderately advanced active pulmonary tuberculosis. The aspirated peritoneal fluid was negative for tubercle bacilli on smear and culture. It is evident that the finding of tubercle bacilli in the marrow was an aid in the differential diagnosis of tuberculous peritonitis and Laennec's cirrhosis. Likewise, in patient E. L. S. the etiology of the panmyelophthisis was quite apparent after the bone marrow aspiration since, not only were tubercle bacilli found on the smear of the processed bone marrow material, but also the stained sections of the marrow revealed caseous miliary tubercle formations.

In Wilson's monograph, he concluded that tuberculous bacillemia was "rare in the early stages of pulmonary and non-pulmonary tuberculosis," occurred in 5 to 10 per cent of "severe, advanced and progressive cases" and was demonstrable in 30 to 40 per cent of cases of miliary and meningeal tuberculosis. The results of the present study are not in complete agreement with these conclusions. In fact, the writers agree with Rich (13), who postulates that tuberculous individuals have periods of bacillemia and that it is not a continuous process but more intermittent. He states that careful study of serial sections of post-mortem material of tuberculous patients who met accidental deaths reveal isolated miliary tubercles of various ages. He quotes the work of several authors who performed extensive histologic examinations on tuberculous cadavers and found miliary tubercle formations in 70 to 100 per cent. Rich concludes that repeated daily studies of the blood of patients with chronic pulmonary tuberculosis probably would reveal that tuberculous bacillemia occurred in 90 to 95 per cent of these people.

According to Rich, the sequelae of the tuberculous bacillemia depend to a great extent on the "increased clearing capacity" of the blood, namely, the ability of the blood to clear itself of circulating organisms and the varying susceptibility of the body organs to the tubercle bacilli. As an aid in the diagnosis of these sequelae, the study of the bone marrow offers definite potential possibilities.

SUMMARY

A preliminary report is made on the use of bone marrow aspirations in the diagnosis of tuberculosis. The procedure is innocuous, rapid, and of definite diagnostic value in establishing the early diagnosis of tuberculous bacillemia and its sequelae, including tuberculous meningitis. Tubercle bacilli was demonstrated in the bone marrow of 14 of 20 patients by direct examination of aspirated material. In 5 of the 14, the diagnoses were also obtained by culture.

SUMARIO

Bacilos Tuberculosos en la Médula Osea

Esta comunicación preliminar se basa en el empleo de aspiraciones de la médula ósea en la tuberculosis. El procedimiento es inocuo, rápido y posee valor diagnóstico bien definido para el establecimiento del diagnóstico temprano de la bacilemia tuberculosa y de sus secuelas, incluso la meningitis tuberculosa. Comunícanse los resultados obtenidos en 20 casos, 70 por ciento de los cuales resultaron positivos para bacilos tuberculosos.

RESUME

Le bacille tuberculeux dans la moelle osseuse

Ce rapport préliminaire est fondé sur l'emploi du prélèvement de la moelle osseuse par ponction, dans la tuberculose. Le procédé est sans danger, rapide et de valeur diagnostique définie en ce qu'il permet d'établir un diagnostic précoce de la bacillémie tuberculeuse et de ses séquelles, y compris la méningite tuberculeuse. Les résultats obtenus dans 20 cas sont rapportés, chez 70 pour cent d'entre eux, la recherche du bacille tuberculeux a été positive.

Acknowledgment

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Editorial

The Specificity of the Tuberculin Reaction

Few procedures employed in the campaign to eradicate tuberculosis have been of greater value than the tuberculin test. It has been useful in the diagnosis of tuberculosis in the individual patient and priceless in studying the epidemiology of the disease and laying foundations for public health practice in tuberculosis control.

It has been of special value in determining the incidence of development of tuberculous infection in exposed groups, such as nurses and other personnel in hospitals and sanatoriums, and studies of the tuberculin reaction in nurses have been of extraordinary service, as will be brought out later in this editorial, in defining the limitations set by nature on the specificity and reliability of the tuberculin reaction as evidence of true tuberculous infection.

It is axiomatic in modern medicine that specific tests must be quantitative. The earliest type of tuberculin test, devised by von Pirquet, was far from quantitative, but the Mantoux test, introduced shortly afterward, supplied the quantitative aspect lacking in the former. With the introduction of purified protein derivative (PPD), the highly active protein principle extracted from culture filtrates of tubercle bacilli grown upon chemically defined nonprotein media, which is itself being still further purified at the present time (Seibert, F. B.: Am. Rev. Tuberc., 1949, *59*, 86), the tuberculin test was still more highly refined from the quantitative point of view. Without a standard tuberculin, permitting accurate comparison of tuberculin tests at different times and different places, analyses of results on the specificity and stability of the tuberculin reaction, which have been frequent in recent years, would have little meaning.

The specificity of the tuberculin reaction has been called into question not a few times. Those who have followed the literature on the epidemiology of tuberculosis during the last fifteen years will recall the serious doubts cast upon the validity of the tuberculin reaction by Lumsden and his colleagues (Am. J. Pub. Health, 1939, *29*, 25) as a result of their failure to correlate tuberculin reactions and the calcifications of supposed primary tuberculosis in a long series of investigations in two intensively studied areas in Tennessee and Alabama. The later surprising correlation of incidence of pulmonary calcification with reaction to histoplasmin, in contradistinction to reaction to tuberculin, and other evidence indicating that the calcifications in question are probably residues of histoplasmosis or other infections conferring sensitivity to histoplasmin (Christie, A., and Peterson, J. C.: Am. J. Pub. Health 1945, *35*, 1131; Palmer, C. E., Pub. Health Rep., 1945, *60*, 513), has been one of the triumphs of epidemiologic research in this country. As a result of elucidation of the calcification puzzle, confidence in the specificity of the tuberculin reaction not only recovered lost ground, but emerged to a higher level than before.

However, not all problems relating to the specificity of the tuberculin reaction have been solved in the important investigations just cited. Indeed, certain

remaining problems have been thrown into bold relief. Chief among these is the relative specificity of low and high doses of tuberculin. There has never been great doubt as to the significance of strong reactions to weak doses of tuberculin. The correlation of such reactions with recent demonstrable active or progressive tuberculous infection is too clear to miss. However, a correlation of weak reactions to strong doses of tuberculin with evidence of past or inactive tuberculous infection has been hard to establish. The general assumption has been that allergic levels vary enormously in different people at different times, and that high doses of tuberculin may be necessary to bring forth evidence of true tuberculous infection in persons natively sluggish in allergic response, or low in sensitivity because of a long lapse of time since the period of progressive sensitizing infection.

Numerous established facts support this assumption. Racial variations in sensitivity are well known; Negro subjects, for example, tend to react to tuberculin more vigorously than white persons. Variations in physiologic state, of remarkable variety, are known to modify the intensity of the reaction. Included among these are nontuberculous infections, pregnancy, hormonal influences, and nutritional factors, such as the tissue concentration of vitamin C. The studies of Dahlstrom (Am. Rev. Tuberc., 1940, *42*, 471) and others have established the effect of time on the reaction. His results indicated that originally weak sensitivity tends to fade in the course of years, and strongly suggested that the vigorous reactions so frequently observed in intimate contacts of persons with open tuberculosis are not the result of a single early subclinical infection of the exposed individual, but rather the aftermath of a constant stimulation of sensitivity by repeated subclinical infections. The results of Aronson (Am. Rev. Tuberc. 1951, *63*, 121) who was impressed by an almost regular rise in sensitivity from the low level conferred by BCG inoculation to a high level in vaccinated persons in contact with cases of tuberculosis, are of similar import. Finally, the low degree of sensitivity conferred by BCG itself is incontestable evidence that the microorganisms as well as the factors of time and constitutional character are concerned in the level of tuberculin sensitivity in different individuals.

Thus, reasons in abundance are at hand to explain variability in sensitivity to tuberculin. But a number of puzzles have remained, for which, fortunately, possible solutions are now in sight. Among these are the weakness and inconstancy of tuberculin reaction in some persons known to be in occasional contact with tuberculous patients, and the great frequency, in certain regions, of tuberculin reactions of low intensity in persons not believed to be in contact with tuberculosis.

A paper by Tukey, DuFour, and Seibert, recently published in this journal (1950, *62*, 77), throws light on the first of these problems. Serial tuberculin tests in a large number of student nurses routinely tested at three-month intervals in a three-year hospital training course revealed a small cumulative increase in the incidence of reactions to the first-strength test dose of PPD (0.00002 mg.), which logically might be attributed to true tuberculous infection, and also a remarkable fluctuation in sensitivity to the second dose (0.005 mg.), from negative to positive and again to negative, in a large number of students who never reacted

to the first dose. The repeated injections themselves appeared to be ruled out as a cause of sensitivity, for no significant cumulative increase in the number sensitive to the second dose occurred, although some subjects were tested more than thirty times, and some reactors to the second dose became negative again in spite of repeated injections of tuberculin. The authors came to the cautious conclusion that their exhaustive analysis "gave no evidence against the hypothesis that these changes in sensitivity are, at least in considerable part, due to slight infection and gradual recovery."

However, the possibility remains open that another cause of sensitivity is concerned. In a recent communication on the longevity of tuberculous patients in the same city, Teague and Placentra (in press) called attention to the fact that during the last 20 years in Philadelphia studies with the standard tuberculin PPD in representative high schools in different parts of the city have shown a steady and striking decline in the incidence of reaction to the first dose of PPD, but very little drop in the incidence of reaction to the second dose. The drop in incidence of reaction to the first dose could be correlated readily with the decline in mortality from tuberculosis, but it is difficult to explain the persistence of a high level of sensitivity to the second dose except on the basis of some other form of sensitivity than that responsible for the typical reaction to the first dose.

These studies, like many others, suggest that organisms other than the tubercle bacillus may be responsible for some, or even the majority, of reactions in second-dose reactors who are insensitive to the first dose. This view recalls the well-known problem of the "no visible lesion reactor" in cattle. Actually "no visible lesion reactors" are sometimes "skin lesion reactors" suffering from minor infectious processes of the skin, apparently due to acid-fast bacteria of very low virulence occurring in soil and grass. Numerous studies on this subject were reported in the twenty years following the early observations of Traum in 1916 (see review by Mohler: Journal-Lancet, 1938, *58*, 183) but the question of nonspecificity of the tuberculin reaction in this respect has not yet been entirely clarified.

The suggestion that other bacteria than the tubercle bacillus may be responsible for nonspecific reactions to tuberculin in man, particularly reactions of the low-sensitivity type seen in persons who fail to react to 0.0001 mg. PPD, but do react to 0.005 mg., has been made by Palmer and Peterson (Pub. Health Rep., 1950, *65*, 1) and Palmer, Ferebee, and Peterson (Pub. Health Rep., 1950, *65*, 1111) after an exhaustive analysis of a long series of tuberculin reactions in nurses in 29 states of the United States. These studies, carried out by the Public Health Service, with support over a period of years from the medical research program of the National Tuberculosis Association, have brought to light certain extraordinary geographic variations in the pattern of reaction to tuberculin. In general, they showed a significant correlation between tuberculosis mortality rates and frequency of reaction to the first dose of tuberculin. The frequency of reaction to the first dose was consistently higher also in urban than in rural communities, a fact suggesting that contact with other human beings is concerned. Reaction to the second dose in subjects failing to react to the first dose was much more

frequent in eight states of the south and southeast, extending from Texas to North Carolina, than anywhere else in the United States and of extraordinary frequency in a region comprising the states of Louisiana, Mississippi, and Tennessee. There was no correlation of reactions of this type with other evidence of tuberculous infection or with the frequency of reaction to the first dose of tuberculin. Moreover, within the specified areas, the level of second-dose sensitivity was remarkably uniform despite substantial variations in the percentages of first-dose reactions. These facts, and a number of others for which the original papers must be consulted, led the authors to the conjecture than an organism different from, but allergenically resembling, the tubercle bacillus is concerned. The geographic pattern and rural relationship suggested that climate and vegetation may be of importance. As a clue, attention was called to the fact that, in general, the region of high prevalence of the low-sensitivity reaction is composed of low-level land with subtropical vegetation, a relatively warm and moist climate, and predominance of a certain type of soil.

The analysis is highly suggestive and stimulating. There can be no disagreement with the suggestion of the authors that the "results of this study would appear to justify a serious search" to learn the nature of the agent concerned. If such search is as successful as the related investigation that uncovered the close relation of pulmonary calcification to reaction to histoplasmin, it will be well rewarded.

Aronson's studies (Am. Rev. Tuberc., 1951, *63*, 121) to which reference was made in a preceding paragraph, also showed a striking geographic correlation with low and fluctuating tuberculin sensitivity. He, too, believed that many such reactions were "nonspecific" and suggested the possibility that acid-fast saprophytes were responsible. He was more inclined, however, to implicate other factors which varied with climate.

There is acceptable experimental evidence to indicate that inoculation of acid-fast saprophytes, acid-fast bacilli of cold-blooded animals, and other types of "paratubercle bacilli" will sensitize animals to tuberculin (Saenz, Crawford, and others; see review by Hauduroy: Inventaire et Description des Bacilles Paratuberculeux, Masson et Cie., Paris, 1946). In view of certain similarities in chemical composition, well worked out in the long series of investigations on the chemistry of the tubercle bacillus sponsored by the National Tuberculosis Association, this fact is not surprising.

We are thus left with two important possibilities in explanation of weak and fluctuating reactions to tuberculin. The first is that these reactions may represent responses to occasional intermittent slight infections with true tubercle bacilli, which heal without leaving visible evidence of their occurrence. The ultimate loss of sensitivity in reactors with a definite history of exposure to tuberculosis after the contact is discontinued and the low level and not infrequent waning of sensitivity after BCG vaccination furnish strong evidence that this possibility is a real one.

The other explanation for the weak and fluctuating reaction is infection by acid-fast microorganisms other than the tubercle bacillus. Evidence in favor

of this is indirect, but nonetheless suggestive. A direct attack on the problem is possible, however, through experiments on sensitization of man by such bacilli and investigation of low-sensitivity reactors for infestation with acid-fast bacilli that might be responsible for the reaction. Certain studies are known to be under way on this problem and it is to be hoped that additional productive programs will be undertaken.

ESMOND R. LONG

BOOKS

ÉDOUARD RIST: *Les Symptômes de la Tuberculose Pulmonaire et de ses Complications. Clinique, Physiologie Pathologique, Thérapeutique. Nouvelle edition entièrement refondue et considérablement augmentée. Pp. 984, 22 illustrations, Masson et Cie., Editeurs, Paris, 1949, 1,800 French francs, or approximately $5.25.*

This is a book of wisdom. The title, though long, is still inadequate. For in addition to its great scientific value it reveals the personality of a phthisiologist of international fame and the manner and method through which he has acquired his outstanding position in the field of tuberculosis. As a practitioner of life-long experience he discounts in no degree the value of modern more mechanical diagnostic methods, but recalls effectively to his colleagues' attention the value of symptomatic contributions to both diagnosis and treatment. Symptomatology serves several purposes. First, it recognizes the fact that tuberculosis is not a disease of the lungs alone but of the patient as a whole. Second, careful examination of symptoms and their skillful evaluation is not only of diagnostic importance but gives opportunity for the physician to establish relations with, and understanding of, the whole person with whom he is dealing. Third, possible complications of other organs, whether tuberculous or not, may be revealed symptomatically that could have a significant bearing on diagnosis.

This volume, almost 1,000 pages in length, is a second edition. The first edition was reviewed by Dr. Max Pinner (Am. Rev. Tuberc., 1945, *52*, 165). The present edition, in which the subject of complications is added to the previous title, is divided into three parts, viz., Functional Symptoms, General Symptoms, and Aberrant Symptoms and Complications. The fifty chapters, twenty more than in the first edition, give in the simple but delightful style of a profound scholar the summary of a long life's fruitful study of tuberculosis. The new material includes a discussion of edema, erythema nodosum, gynecologic relations to symptoms, and a very important section on psychiatric aspects of tuberculosis.

The author apologizes for frequent personalization of the account, but justifies it on the ground that it is his "scientific testament." If so, it is a valuable one. The book may be read with profit and genuine pleasure by all physicians interested in the immediate or differential diagnosis of tuberculosis.

KENDALL EMERSON

KENNETH W. HAMILTON: *Counseling the Handicapped in the Rehabilitation Process. Pp. 296, The Ronald Press, New York, 1950, $3.50.*

The principle of rehabilitation is familiar to all physicians and is indeed as old as the practice of medicine. The average physician is likely to find himself unable to proceed with the rehabilitation of the patient for the simple reasons of lack of time and lack of necessary information. He may do an excellent job in diagnosis and management of his patient from the medical standpoint but obtain a poor result because of his inability to handle some aspect of the patient's rehabilitation.

Inasmuch as rehabilitation usually involves assistance from the doctor, physiotherapist, psychiatrist, social service worker, employee counsellor, occupational therapist, and others, it is next to impossible to effect rehabilitation by referral to all of these individuals. Even if such were possible, it would be unlikely that coordinated activities could

take place to the patient's benefit. In the end the doctor is inundated with many forms to be filled out. The book under discussion is an attempt to describe rehabilitation, to delineate its functions, and to describe means of coordinating the efforts of the rehabilitation team. It represents the first step in the organization of activities, the end of which is a socially and economically functioning patient.

The doctor needs a "locus" to which the handicapped patient may be referred, not for charity, but for constructive dealing with the problems remaining after diagnosis and definitive medical therapy have been completed. The "locus" may be an institute, a hospital committee, or a nonmedical coordinator. The contents of this book suggest that adequate means of dealing with these problems will be available in the future. The interested physician will find encouragement in reading this book.

GEORGE A. WOLF, JR.

W. C. CUTTING AND OTHERS (editors): *Annual Review of Medicine. Pp. 484, Volume 1, 1950, Annual Reviews, Inc., Stanford, California, $6.00.*

The purpose of these volumes is to review regularly the work in the various spheres comprising medicine, the more active categories being considered annually. The material contained in this volume is designed to review contributions to medicine made, for the most part, from 1947 through 1949. Sufficient background information is included in each section for orientation of the physician unfamiliar with recent trends of investigation in a particular field.

This book contains twenty-one sections, each concerned with reviewing the recent developments in clinical medicine. The material covered in the more active fields of investigation is somewhat selective, as limitation of space forbids a comprehensive survey of all aspects of a particular subject. Therefore, it is most important that the authors have been selected from the active contributors to the literature in recent years. The interpretation of the relative significance of new material by qualified authors will be greatly appreciated by the physician. Nevertheless, this assessment of the work discussed must at times neglect certain aspects which the reader may be particularly interested in having stressed.

The text of each section is easily readable. For those who desire a more detailed account of a particular contribution, an extensive bibliography is included. In addition, there is an excellent annotated list of reviews pertaining to the topics covered in this volume. The book also contains an author index as well as a comprehensive subject index.

This book will prove invaluable to those interested in keeping abreast of the rapidly unfolding advances in medicine.

CHARLES LE MAISTRE

KATHLEEN NEWTON: *Geriatric Nursing. Pp. 480 with illustrations, The C. V. Mosby Company, St. Louis, Missouri, 1950, $4.50.*

The author of this first book on geriatric nursing has done a real service by bringing into focus the application of nursing knowledge and skills to the care of the aged. Balanced consideration has been given throughout to fulfilling needs of the aged for day-to-day comfort and to adaptations of nursing which will promote therapeutic measures.

The first part of the book emphasizes how the aged feel about themselves and current social attitudes, customs, and institutions which affect their well being. The second part

deals with general hygiene and nutrition of the aged. The third and last part is devoted to specific diseases, the problems they create for the aged patient and the nurse, and the adaptations of nursing care which are needed.

The well-selected illustrations, the documentation, the discussion of specific needs of the aged, together with explicit suggestions for nursing care, and the author's apt and interesting way of expressing herself make this book both readable and useful.

Repetitious emphasis on the loneliness of the aged undoubtedly has been deliberate but may tend to defeat its purpose by wearying the reader. Certainly, there is need to arouse us all to awareness that "our sentimental concern for them (the aged) is not sustained by our actions."

The appearance of this book at the time of the National Conference on Aging, in Washington, D. C., August 1950, seems particularly fortunate.

KATHARINE G. AMBERSON

BOOKS RECEIVED

THE MERCK MANUAL. Eighth edition. By various authors. Pp. 1,592, Merck & Co., Inc., Rahway, New Jersey, 1950, Price, $4.50, regular edition; $5.00, thumb-indexed edition

THE MANAGEMENT OF THE PATIENT WITH SEVERE BRONCHIAL ASTHMA. By Maurice S. Segal. Pp. xv–158, 16 illustrations, Charles C Thomas, Springfield, Illinois, 1950, Price, $3.50

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PNEUMOCONIOSIS. Edited by Arthur J. Vorwald. Pp. 659 with illustrations, Paul B. Hoeber, Inc., New York, 1950, Price, $7.50

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YOU'RE HUMAN, TOO. By Adele Streeseman. Pp. 206, Coward-McCann, Inc., New York, 1950, Price, $3.00

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ABSTRACTS

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CLINICAL STUDIES, TUBERCULOSIS

Apical Scars.—Pulmonary apices were examined microscopically in a series of 40 autopsies. Seventeen scars were discovered. One showed nodular silicosis; 2 were characteristically tuberculous; the remaining 14, the common type of apical scar, showed intact alveolar pattern without thinning of the pleura but with alveolar spaces moderately collapsed and containing fine strands of fibrous tissue. This common type of apical scar with intact alveolar patterns is attributed to an organized pneumonia which in most cases is not tuberculous.—*Apical pneumonic scars, H. A. MacMillan, Arch. Path, November 19, 1949, 48: 577.—(E. Bogen)*

Miliary Tuberculosis in Children.—There are many references to unexpected postmortem findings of miliary tuberculosis in patients with normal ante-mortem chest roentgenograms. Because the diagnosis of this condition during life has become almost exclusively a roentgenographic one, an attempt was made to investigate the accuracy of this method of diagnosis. In a series of autopsies the diagnosis of miliary tuberculosis was made in 32 children under the age of 14; in all but 2, there was concomitant tuberculous meningitis. An additional 11 children died from tuberculous meningitis without miliary tuberculosis. Chest roentgenograms taken within two weeks of death were available in all instances. In all but 4 children, the fundus oculi had been studied for choroidal tubercles. In 12 of these 52 cases, miliary tuberculosis had been diagnosed roentgenographically before death, and choroidal tubercles were seen in 10 of the 11 of these cases examined funduscopically. At necropsy these cases all showed macroscopic miliary tubercles numbering 5 to 20 per cm.^{2}; on histologic examination these measured more than 0.5 mm. in diameter. In the remaining 40 cases, miliary tuberculosis was not diagnosed roentgenographically, although in 6 instances it had been diagnosed earlier prior to institution of streptomycin therapy. In 5 of these 6 cases, choroidal tubercles had been present, so that of 17 patients with miliary tuberculosis diagnosed by chest films, 15 had choroidal tubercles. In 34 children no roentgenographic evidence of miliary tuberculosis was present; choroidal tubercles were present in only 10 of the 31 patients in this group examined funduscopically. The pulmonary lesions varied from 1 to 6 per cm.^{2} and the majority measured less than 0.5 mm. in diameter. Therefore, miliary tuberculosis was diagnosable by roentgenography in only 18 of 52 cases, by the presence of choroidal tubercles in 25 of 48 children examined funduscopically, and by one or both methods in 28 of the 52 cases. There was no correlation between the histologic structure of the tubercle and the ability to make a roentgenographic diagnosis; the size and numbers of tubercles were thought to be the determining factors. The high incidence of negative roentgenograms was perhaps tempered by the fact that all of these patients died from tuberculous meningitis and that with a longer survival period the pulmonary lesions might have become visible roentgenographically. The presence of choroidal tubercles which develop early in the disseminating phase is thought to be of great aid in the early diagnosis of miliary tuberculosis. These lesions were not present in the 11 cases of tuberculous meningitis in which pulmonary miliary dissemination was absent.—*Radiological and pathological correlation of miliary tuberculosis of lungs in children with special reference to choroidal tubercles, J. L. Emery, & J. Lorber, Brit. M. J., September 23, 1950, No. 4681: 702.—(E. A. Riley)*

Infrapulmonary Pleural Effusion.—Atypical collections of pleural fluid are frequent but their true nature may not be appreciated. One of the least frequent locations for atypical pleural effusion is between the base of the lung and the dome of the diaphragm. In the case of a 25-year-old Negro male patient, diagnostic pneumoperitoneum helped to establish the diagnosis. Subsequent thoracentesis and the finding of tubercle bacilli on culture from this fluid confirmed the clinical impression of the tuberculous serifibrinous pleurisy. In a previous group of 12 cases of infrapulmonary pleural effusion, 6 occurred during known tuberculosis, 2 were due to malignancy, one was in a cardiac patient, one was a postpneumonic empyema, and 2 were of unknown cause. Differential diagnosis usually must include subphrenic abscess, enlarged liver, diaphragmatic hernia, tumors of the lung, mediastinum, and pleura, basal lung cysts containing fluid, and atelectasis.—*Infrapulmonary pleural effusion, E. Rothstein & F. B. Landis, Brit. J. Radiol., August, 1950, 23: 490.*—(*B. Hyde*)

Tuberculous Otomastoiditis.—Tuberculous otomastoiditis occurs more commonly among children than adults. Five cases are here reported in children and 3 in adults. Tuberculous infection of the ear may be either primary or secondary but it is almost always of the latter type. The route of infection is controversial. The ear may be infected by way of the eustachian tube, through the blood stream, or by lymphatic spread. The primary focus can usually be found in the lungs, genitourinary system, or bones. In 5 of the 8 cases, the lungs contained tuberculosis but tubercle bacilli never were found in the sputum; the ear infection was most probably from the blood stream. The development of postauricular fistulas or sinuses and the presence of facial paralysis are very common in tuberculous otomastoiditis. Five of the 8 cases had this complication. The tuberculous etiology of otomastoiditis can be established through cultural or biopsy methods. Treatment consists of general hygienic measures, treatment of the primary tuberculous focus, local therapy as for common ear infections, radical mastoidectomy when surgery is indicated, and streptomycin intramuscularly. No streptomycin was available for treatment in the 8 cases reported. —*Tuberculous oto-mastoiditis with a report of eight cases, S. C. Hisiao, Chinese M. J., May-June, 1950, 68: 149.*—(*L. Hyde*)

ACTH and Tuberculosis.—Rapid defervescence and subsidence of systemic manifestations occurred in 4 acutely ill tuberculous patients treated with adrenocorticotrophic hormone. Laryngeal lesions could be seen by direct observations to heal. With the discontinuation of therapy, all of the symptoms promptly returned.—*Effects of ACTH on tuberculosis in humans, R. Tompsett, C. Le Maistre, C. Muschenheim, & W. McDermott, J. Clin. Investigation, June, 1950, 29: 849.*—(*S. Hadley*)

Complications after Pneumonectomy.—In the period 1947 to 1949, 120 pulmonary resections were carried out, with a mortality of 6 per cent during the first week after operation. The major complications occurring at a later date were empyema and bronchial fistula. The 13 deaths which occurred during the observation period were all due to these two causes; none to contralateral spread. Two cases of early bronchial fistula developed before the end of the second week; 24 cases of empyema were detected two to six weeks after operation, of which 15 were simple empyema and 9 were combined with bronchial fistula; 5 bronchial fistulas occurred, three to seven months after pneumonectomy. The incidence of these complications is higher than that reported by American and British authors. This is attributed in part to the large proportion of "poor risk" cases including cases of "destroyed lung," of giant cavities, of combined pleural and pulmonary involvement, and of disease due to streptomycin-resistant bacilli. Of 15 post-pneumonectomy cases of empyema without bronchial fistula, 13 were cured by thoracoplasty. There were 10 deaths in the group of 11 patients with early empyema and bron-

chial fistula. If bronchial fistula occurred after the fourth month the prognosis was less grave; in 4 of 5 cases thoracoplasty was successful.—*Empyèmes et fistules bronchiques secondaires et tardives dans l'exérèse pulmonaire pour tuberculose (la prévention et le traitement de ces complications)*, *M. Bérard, J. C. Sournia, & M. Jaubert de Beaujeu, Rev. de la tuberc., 1950, 14: 818.*—(*V. Leites*)

Thoracic Surgery for Tuberculosis.—During a two-year period in a French sanatorium, 328 extrapleural pneumothoraces (of which 17 were bilateral), 169 stages of thoracoplasty, and 3 pneumonectomies were performed, with no deaths during the three weeks following operation. Two-thirds of the patients were good or fairly good risks; the remainder were poor or very poor risks. One-half of the patients had bilateral disease; in 20 per cent there was contralateral collapse before the surgical intervention. After thoracoplasty 8 patients had complications, mostly involving the lung base with congestion or bronchial stasis, atelectasis, or rapid development of a tuberculous focus. All of these complications were of a transitory nature. After extrapleural pneumothorax the chief complication was hemorrhage; in 17 cases this was severe and occurred early, most often 36 hours postoperatively. All of these patients were immediately operated upon again and recovered. In an adtional 26 patients, clotted blood, organised hemorrhagic effusion, or fibrin deposits were removed surgically. This intervention was usually performed between the sixth and eighth days and was a simple procedure.—*Chirurgie de la tuberculose pulmonaire en milieu sanatorial (cinq cents interventions consécutives sans mortalité opératoire)*, *M. Bérard, Jacquemet, A. Carraud, Mons, & Ray, Rev. de la tuberc., 1950, 14: 719.*—(*V. Leites*)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Calcifying Histoplasmosis.—Recent evidence shows that histoplasmosis is present as a mild asymptomatic disease which is quite prevalent in certain geographic areas. The principal significance of this silent process is that in certain respects it resembles tuberculosis so closely as to be frequently confused with it. In both diseases there are identical pulmonary calcifications but some occur in people hypersensitive to tuberculin and others in persons hypersensitive to histoplasmin. The antecedent lesion in such tuberculosis is a soft infiltrate in a tuberculin-positive individual from whom it is frequently possible to recover tubercle bacilli. Similar soft lesions have been found in histoplasmin-positive, tuberculin-negative persons and the fungus *Histoplasma capsulatum* has been recovered in some cases. By periodic routine roentgenographic and skin testing in Kansas City, several hundred histoplasmin-positive, tuberculin-negative children with pulmonary infiltrates were found. These children have now been followed for as long as four years during which time some of the infiltrates disappeared completely, some became fibrotic, and the majority gradually calcified. All the 17 children, whose serial chest films are shown in this report, were completely asymptomatic throughout the period of observation, with no history of any illness which could be related to the development of the infiltrate. All the children remained hypersensitive to histoplasmin and negative to tuberculin. The precalcific lesions are classified as (*1*) disseminated infiltrates consisting of multiple lesions scattered throughout both lung fields, marked hilar adenopathy usually being associated with this type of involvement; (*2*) pneumonic infiltration, usually consisting of small, poorly circumscribed, irregular areas, and (*3*) nodular foci, varying from 0.5 to 4 cm. in diameter.—*Development of calcification in pulmonary lesions associated with sensitivity to histoplasmin*, *M. L. Furcolow, Pub. Health Rep., November, 1949, 64: 1363.*—(*E. A. Rouff*)

Pneumonia in Infancy and Childhood.—A review of 214 cases of pneumonia in infants and children was undertaken to ascertain the relative efficacy of sulfonamide, penicillin, and combined therapy. Mortality for all forms of treatment was 17 per cent and most of these occurred in the age group less than six months

of age (28 among 76 infants). In the group more than six months of age, there were 5 deaths in 118 cases. A combination of sulfonamides and penicillin does not appear to be any more effective than either drug alone. Any attempt to reduce mortality rate must be directed towards improved treatment during the first six months of life. Of 20 patients who died within 24 hours after admission, 15 were less than six months of age and all were artificially fed. Leukocyte counts were studied and no prognostic significance could be attributed to total white count or to percentage of polymorphonuclears.—*The prognosis of pneumonia in infancy and childhood, A. Holzel & B. Wolman, Arch. Dis. Childhood, September, 1950, 25: 282.*—(*L. Levin*)

Lesions Resembling Boeck's Sarcoid.—The microscopic pattern of the granulomatous lesion known as Boeck's sarcoid is not necessarily pathognomonic for sarcoidosis. A wide variety of agents, including the unknown cause of sarcoidosis, seem capable of inducing the characteristic granuloma, and it has become increasingly evident that a careful distinction must be made between the "sarcoid lesion" and the disease "sarcoidosis." The association of sarcoid-like lesions with neoplastic disease is apparently less well known. Five cases are here reported in which sarcoid-like lesions were noted in the lymph nodes draining areas containing malignant neoplasms. The primary lesions were a carcinoma of the soft palate, a growth which probably was melanocarcinoma, on the forehead, carcinoma of the breast, adenocarcinoma of the ampulla of Vater, and a cylindroma of the bronchus. In none of the 5 cases was there evidence of systemic sarcoidosis. The striking morphologic similarity between the sarcoid-like lesions observed in neoplastic or non-neoplastic disease and the so-called true sarcoid lesions of the systemic disease suggests that there may be etiologic factors common to both. The similarity in the pattern of the hosts' response may be of greater significance than possible viral, bacteriologic, or specific chemical reagents in the development of this granulomatous process, systematically or locally.—*Lesions resembling Boeck's sarcoid in lymph nodes draining an area containing a malignant neoplasm, E. M. Nadel & L. V. Ackerman, Am. J. Clin. Path., October, 1950, 20: 952.*—(*J. S. Woolley*)

Hodgkin's Disease of Lung.—Primary Hodgkin's disease of the lung is rare. The probable sources are the lymph nodules in the parenchyma of the lung and the submucosa of the bronchi. Secondary Hodgkin's disease of the lung is more common, originating in the mediastinal lymph nodes. The lesions are radiosensitive. Irregular fever, anemia, and loss of weight are usually found. A 52-year-old white male was admitted with the symptoms of malaise, weakness, and sore throat. A chest roentgenogram showed a moderate amount of fibrosis in both lung fields and thickening of the apical cap on the right side. Biopsy of an axillary lymph node revealed chronic toxic lymphadenitis with fibrosis. The patient was readmitted eleven months later, complaining of productive cough, weakness, and fever. The sputum was blood tinged. A chest roentgenogram showed many small areas of infiltration throughout both lung fields, coalescing in the middle and lower lobes of the right lung and the upper lobe of the left lung. The patient died soon after admission. The anatomic diagnoses were: carcinoma of the lungs, right pleural effusion, bilateral lobar pneumonia. The histologic diagnosis was: primary Hodgkin's disease of the lungs and occasional Hodgkin's nodules in the liver.—*Primary Hodgkin's disease of the lung, K. Yardumian & L. Myers, Arch. Int. Med., August, 1950, 86: 233.*—(*G. C. Leiner*)

Diagnosis of Lipoid Pneumonia.—The number of reported cases of lipoid pneumonia is increasing and a simple method of diagnosing it is needed. One such method was tested, using a group of 20 patients with findings suggestive of lipoid pneumonia and a control group of 45 other patients. The patients were kept on a strict fat-free diet before and during the period of the test. A 24-hour collection of sputum was obtained daily for three to five

consecutive days. Six slides were prepared from each specimen. Three were stained with Sudan IV and 3 with Wright's stain as modified by Lillie. The sputum was considered positive if the Wright stain showed characteristic vacuoles in the macrophages, and if these vacuoles stained orange-brown with Sudan IV, or if abundant extracellular fat-staining material was noted. Microscopic examination was made also of material aspirated from the lungs of all but one of the positive patients. Lipoid material was found in the sputum of 19 of the 20 patients suspected of having lipoid pneumonia, and of 2 of the 45 patients in the control group. The lung aspirations confirmed the findings in the sputum. Most of these patients had diseases of the central nervous system and some had rheumatoid arthritis. All but 2 had previously taken mineral oil or nose drops over a period varying from two to thirty years, either continually or at intervals. Five had no respiratory symptoms whatever, and the diagnosis of lipoid pneumonia was made during routine roentgenographic study of the chest. The remaining patients had had intermittent productive cough.—*Diagnosis of lipoid pneumonia by examination of sputum, S. Losner, B. W. Volk, W. R. Slade, L. Nathanson, & M. Jacobi, Am. J. Clin. Path., June, 1950, 20: 539.*—(*J. S. Woolley*)

Pulmonary Hemosiderosis in Cardiac Disease.—In a case of mitral stenosis, roentgenograms of the lungs showed a miliary type of infiltration. The changes were remarkably constant over a period of seven months. Necropsy showed that the shadows were due to deposits of hemosiderin. Since then, the authors have been observing other patients with cardiac disease. There were none in whom the changes were as conspicuous as in the first, but in one or 2 they were fairly striking and in others, less definite. In still others, with normal lung fields roentgenographically, there were typical necropsy changes. In all, evidence of hemosiderosis was found at necropsy in 26 of 33 cases of mitral stenosis. On the surface of the lungs, the deposits appear to be dark bluish spots. On the cut surface, they are found actually to be dark brown. They are easier to see in lungs containing relatively little carbon. Microscopically, the nodules are found to be distributed haphazardly within the alveolar zones of the lung without relationship to the bronchi, veins, or septa. A nodule consists of a group of 4 to 20 adjacent alveoli filled with hemosiderin. The transition to adjacent normal alveoli is abrupt. There is no emphysema. The hemosiderin is all within phagocytic cells; none is free. There is also ferrous impregnation of the elastica of small arteries due to excess iron. There is very little capillary congestion. This condition results from hemorrhages into the respiratory bronchioles at the bronchopulmonary venous anastomoses. Under the prevailing abnormal dynamics, these become varicose and tend to bleed. The constancy of the nodules suggests repeated hemorrhages. The picture of pulmonary hemosiderosis is also seen in prolonged left ventricular failure associated with other types of heart disease.—*Pulmonary changes due to cardiac disease with special reference to haemosiderosis, A. C. Lendrum, D. W. Scott, & S. D. S. Park, Quart. J. Med., July, 1950, 19: 249.*—(*A. G. Cohen*)

Pulmonary Telangiectasis.—The disease known as hereditary hemorrhagic telangiectasia is characterized clinically by the triad of telangiectasia, hemorrhages, and familial history. Many organs can be involved, among which are the lungs. The radiologically visible arteriovenous fistulas are only larger counterparts of numerous telangiectases scattered throughout the lungs. The abnormal physiological effects of many small telangiectases may equal that of a large fistula. Two cases are reported. In one, there were numerous small lesions, both in the lungs and elsewhere. In the other, there was a large fistula. In each case, cyanosis was quite severe. It is suggested that the numerous small arteriovenous communications which normally occur in the lung are physiologically quiescent. They may become functionally active in disorders other than telangiectasia.—*Telangiectasis of the*

lungs, A. J. Brink, Quart. J. Med., July, 1950, 19: 239.—(A. G. Cohen)

Funnel Chest.—Funnel chest is thought to be uncommon although many cases have been reported since it was first described in 1600. The defect is congenital and there is a considerable hereditary tendency. It is caused by a short central tendon in the diaphragm, with a deformity and a retraction of the lower end of the sternum during inspiration. It is not always central or symmetrical. Upper respiratory obstructions probably have little to do with etiology. The retracted sternum makes the individual appear round-shouldered, hollow-chested, and pot-bellied. Other congenital deformities may be present. Lung symptoms may be due to an ineffectual cough. Heart symptoms are more common and are the result of, and in proportion to, the pressure of the retracted sternum. A systolic murmur is commonly present. The therapy is surgical, and operation before the end of the first year of age is simple. The next safe period is from two and one-half to five years. At a later age the procedure is more difficult. There were no deaths and few complications in the author's series of 42 operated cases.—*Funnel chest: Its cause, effects, and treatment, C. W. Lester, J. Pediat., August, 1950, 37: 224.—(W. H. Oatway, Jr.)*

Esophageal Achalasia in Newborn.—Three cases of achalasia of the esophagus in the newborn are presented, and the world's literature concerning such cases is reviewed. Clinical symptoms are vomiting and weight loss. The diagnosis is made by radiologic examination, and lipiodol should be used as contrast medium. Treatment has been the use of atropine, gavage, and dilatation by soft rubber catheter, all with variable success. In the main prognosis is good.—*Neuro-muscular incoordination at the cardia in the newborn, J. Thompson, Arch. Dis. Childhood, March, 1950, 25: 52.—(L. Levin)*

Smoking and Bronchogenic Carcinoma.—The marked increase in England and Wales of deaths attributed to carcinoma of the lung between the years 1922 and 1927 is out of all proportion to increase in the older age groups and cannot be entirely due to more accurate methods of diagnosis. The present investigation was planned to ascertain whether patients with carcinoma of the lung differed materially from other patients in respect to their smoking habits. Among 649 male patients with bronchogenic carcinoma, 2 (0.3 per cent) were nonsmokers; among a like number of control patients, 27 (4.2 per cent) were nonsmokers. Among 60 female patients with carcinoma of the lung, 19 (31.7 per cent) were nonsmokers, whereas 32 (53.3 per cent) of a control group of female patients with other diseases were nonsmokers. Apart from the general excess of smokers in the group of patients with bronchogenic carcinoma, there was in this group a significantly higher proportion of heavier smokers and a correspondingly lower proportion of lighter smokers than in a comparative group of other patients. Of the male patients with cancer of the lung, 26 per cent smoked 25 cigarettes or more daily, compared with only 13.5 per cent of the control group. The same trend was observed in women, but the numbers involved were too small to be of statistical significance. It was demonstrated that the patients with bronchogenic carcinoma show a tendency to start smoking earlier in life, to continue longer, and to be less inclined to stop than patients in the control group. Among 525 patients with bronchogenic carcinoma who had smoked pipes or cigarettes but not both, 5.7 per cent were pipe smokers and 94.3 per cent were cigarette smokers, as compared with 9.7 per cent and 90.3 per cent, respectively, in a control group. There was no statistical significance between inhalers and noninhalers. Among patients with different diseases in the control groups, there was no correlation between smoking and diseases of the respiratory tract or between smoking and cancer in other organs. There was no suggestion that the onset of symptoms due to cancer of the lung caused the development of smoking habits which were all established prior to the onset of the illness. The failure to correlate inhalation with the

development of carcinoma may indicate that the size of the smoke particle carrying the carcinogenic agent is the determining factor. There is as yet no evidence regarding the specific nature of this carcinogen. The figures suggest that, above the age of 45, the risk of developing bronchogenic carcinoma increases in simple proportion with the amount smoked and may be approximately 50 times as great among those who smoke 25 or more cigarettes daily as among nonsmokers.—*Smoking and carcinoma of the lung, R. Doll & A. B. Hill, Brit. M. J., September 30, 1950, No. 4682: 7392.*—(*E. A. Riley*)

Cytologic Diagnosis of Lung Cancer.—Cytologic examinations of sputum and bronchial secretions were carried out in 2,066 cases; positive cytologic diagnoses were made in 201. The positive reports were made in cases of proved malignant disease with the exception of 2 false diagnoses of suspicious findings made in cases of lesions proved pathologically to be benign. The over-all percentage of accuracy in 241 cases of proved bronchogenic carcinoma was 55 per cent. When an adequate series of 5 specimens of sputum per patient was examined, the case-finding sensitivity was 90 per cent in 130 cases. Extensive experience is the most important single factor in cytologic diagnosis. The ultimate value of cytologic techniques in the early diagnosis of primary lung cancer remains to be established by further investigative work.—*Evaluation of cytologic diagnosis of lung cancer, S. M. Farber, A. K. McGrath, Jr., M. A. Benioff, & M. Rosenthal, J.A.M.A., September 2, 1950, 144: 1.*—(*H. Abeles*)

Solitary Pulmonary Metastasis.—A 14-year-old boy had a right hemithyroidectomy for papillary adenocarcinoma of the thyroid gland. A solitary, metastatic lesion was demonstrated in the right lung one year after the operation. The uptake of I^{131} in the area of the metastasis following a tracer dose was four times that of an involved control area. Two months after the administration of 78 millicuries of I^{131}, the lung lesion had resolved. Evidence of myxedema was observed two months after the first therapeutic dose. After two additional doses of radioactive iodine (a total of 137 millicuries) there was no evidence of localization or concentration of radioactive iodine within the body. Twelve months after the initial dose of I^{131} and seven months after the commencement of desiccated thyroid therapy, the patient was well and there was no evidence of metastases.—*Pulmonary metastatic lesion successfully treated with radioactive iodine: Report of a case of pulmonary metastasis from a papillary adenocarcinoma of the thyroid, A. S. Freedberg, A. L. Ureles, M. F. Lesses, & S. L. Gargill, J.A.M.A., September 2, 1950, 144: 16.*—(*H. Abeles*)

Temporary Plumbage in Thoracoplasty.—At the Bravo Chico Sanatorium in Lima, 36 cases of pulmonary tuberculosis were treated with thoracoplasties. Between the first and second stages, celluloid ping-pong balls were used for extrapleural packing to secure optimal collapse and to prevent adhesions. The material was removed during the second stage of the operation. With this method, postoperative complications were minimized and the percentage of sputum conversions was higher during the first month after operation. Penicillin and streptomycin were used successfully to prevent infection. Ping-pong balls were chosen for use because of their light weight and because they did not cause unfavorable reactions. The material was sterilized in a dry condition with formaldehyde vapors.—*Uso del plombaje en las toracoplastias, S. Huaco Vizcardo, E. Olivares, & J. Cáceres, Rev. tuberc., July–December, 1949, 9: 209.*—(*A. A. Moll*)

ANTIMICROBIAL THERAPY

Tuberculin and Streptomycin for Tuberculous Meningitis.—The most favorable statistics for tuberculous meningitis treated with streptomycin by the authors showed a mortality of 40 per cent. An analysis of the fatal cases showed the following: (*1*) There were no clinical or laboratory features whereby a prognosis could be given except that, when de-

cerebrate rigidity appeared, the condition was hopeless. (2) Necropsy always revealed at the base of mid-brain an exudate which contained living tubercle bacilli. (3) In treated cases, the cell count in the cerebrospinal fluid fluctuated. This fluctuation might be due to the liberation of tuberculin as the result of the destruction of organisms. To test this hypothesis, tuberculin was injected intraspinally. In tuberculin-negative cases, there was no reaction. In positive cases, there were symptoms and a rise in cell count. The fluid of patients with tuberculous meningitis, however, when used for a Mantoux test on positive reactors failed to evoke a response. Intrathecal tuberculin was then given to 3 patients with tuberculous meningitis in whom decerebrate rigidity had appeared. Remarkably, 2 recovered. In the one that succumbed, survival was exceptionally long. Necropsy showed no exudate at the base of the mid-brain.—*Effects of intrathecal tuberculin and streptomycin in tuberculous meningitis, H. V. Smith & R. L. Vollum, Lancet, August 19, 1950, 2: 275.*—(*A. G. Cohen*)

Streptomycin and Pneumothorax in Tuberculosis.—Of 80 patients with moderately advanced fibrocaseous tuberculosis, 44 were treated with streptomycin alone and 36 with both streptomycin and pneumothorax or, in a few cases, Jacobeus' operation. No significant difference in results was noted between the two series. The effect was favorable in a high percentage of cases, especially from a clinical standpoint. Results seemed to improve as the total dosage of streptomycin was increased. The highest proportion of cases with conversion of the sputum to negative (71.5 per cent) and with clinical and radiologic improvement (85.7 per cent) was found among 6 patients treated with a total dosage of 80 to 99 gm. of streptomycin as well as pneumothorax. Among those not treated with pneumothorax, the best clinical results (100 per cent) were in 13 patients receiving more than 80 gm. of the drug and the best roentgenologic results (66.6 per cent) in 6 patients receiving more than 100 gm. Sputum conversion was uncommon in all the groups treated with streptomycin only. As indications for streptomycin therapy, the following were accepted: an exudative tendency, presence of extrapulmonary complications controllable with the drug, and pneumothorax.—*Informe sobre el tratamiento con estreptomicina en el Hospital Sanatorio No. 1, O. García Rosell, V. M. Tejada, & V. Narváez O., Rev. Tuberc., July–December, 1949, 9: 189.*—(*A. A. Moll*)

Cavities and Streptomycin Resistance.—No correlation was found between the number of tuberculous cavities and the emergence of streptomycin-resistant tubercle bacilli in the sputum during treatment. Of the patients treated for more than 40 days, resistant bacilli occurred in 74 per cent with one cavity and in 76 per cent of those with several cavities. Among patients with cavities less than six months old, resistance developed in 75 per cent as compared to 62 per cent of those with older cavities. The difference was more significant when evaluated according to the degree of activity of the disease; 82 per cent of patients with highly progressive disease developed resistant bacilli as compared to 62 per cent of those whose process was less active.—*La streptomycino-résistance du bacille de Koch dans la tuberculose pulmonaire, G. Canetti & H. Lacaze, Rev. de la tuberc., 1950, 14: 685.*—(*V. Leites*)

Ambulatory Streptomycin Therapy. Of 168 cases of pulmonary tuberculosis treated ambulatorily with streptomycin in a Lima dispensary, 56 were selected for a more complete study. Pneumothorax was also used, mostly before resorting to streptomycin, in a number of cases, especially of the infiltrating type. In all cases, the drug was given intramuscularly in a dose of 1 gm. daily. In fibrocaseous cases, results were better when both streptomycin and pneumothorax were used. The opposite was true in infiltrating cases which fared far better with streptomycin alone. Clinical improvement was the most significant finding in the series as a whole. Roentgenologic improvement was seen chiefly

in tuberculosis of the nodes and lungs and in cases of hematogenous dissemination. Disappearance of tubercle bacilli from the sputum was noted only in ganglio-pulmonary cases.—*Observaciones sobre el tratamiento estreptomicínico en el medio dispensarial, L. A. Madariega Zevallos, Rev. Tubere., July–December, 1949, 9: 260.*—(*A. A. Moll*)

Replacement of Streptomycin-resistant Bacteria.—It is known that after the appearance of streptomycin-resistant tubercle bacilli during treatment, these resistant variants may persist for ten to twenty months after the end of therapy. These authors have studied changes in sensitivity of coliform bacilli in the stools of streptomycin-treated patients. Of 57 stool specimens examined before therapy, only one showed resistant colonies. During treatment, 8 of 11 patients rapidly developed many colonies of *E. coli* which were resistant to 5 γ or more of streptomycin. In the other 3 cases, after the appearance of resistance, predominantly sensitive organisms appeared either temporarily or permanently despite the continuance of the drug. With the cessation of therapy, in all but 2 cases resistant variants had disappeared within two months. That this was not a back mutation is supported by the fact that serial transfers of these resistant strains did not become sensitive again.—*The replacement of streptomycin-resistant coliform bacteria in the stools by streptomycin-sensitive variants during and following the cessation of streptomycin therapy, M. Hamburger & J. Berman, J. Clin. Investigation, May, 1950, 29: 630.*—(*S. Hadley*)

Aureomycin in Experimental Murine Tuberculosis.—*In vitro* aureomycin compared favorably with streptomycin and para-aminosalicylic acid in its antibiotic activity against *Mycobacterium tuberculosis* H37Rv growing in Dubos medium. *In vivo*, aureomycin proved ineffective as a therapeutic antibiotic agent in experimental tuberculosis in dba mice.—*A comparative study of susceptibility of tubercle bacillus (H37Rv) to aureomycin, streptomycin, and para-aminosalicylic acid,—M. M. Steinbach, H. Baker, & C. J. Duca, Proc. Soc. Exper. Biol. & Med., July, 1950, 74: 596.*—(*F. B. Seibert*)

Tb1 in Murine Tuberculosis.—One mg. of *p*-anisaldehyde-thiosemicarbazone (Tb1/698) per 100 cc. inhibited the growth of the H37Rv and B1 strains of *Mycobacterium tuberculosis* in Dubos medium. Mice infected with the H37Rv strain and fed 1 per cent Tb1/698 in their diet had no gross tuberculosis when sacrificed at the end of thirty days when all controls were dead of the disease. Infected mice, sacrificed after seventy-five days of treatment with the drug, showed only one plus gross pulmonary tuberculosis. Tb1/698 may be considered to be an antibacterial agent in the mouse as well as *in vitro*.—*p-Anisaldehyde-thiosemicarbazone in treatment of experimental murine tuberculosis, M. M. Steinbach & H. Baker, Proc. Soc. Exper. Biol. & Med., July, 1950, 74: 595.*—(*F. B. Seibert*)

Antituberculous Activity of Some Chinese Herbs.—The *in vitro* activity of 61 common medicinal herbs against *M. tuberculosis* was examined. Five strains of *M. tuberculosis* and 4 strains of nonpathogenic acid-fast bacilli were used. The crude extract of Coptis root (*Coptis coinensia*) showed marked activity against *M. tuberculosis*. In general, berberine bisulfate, the alkaloid derived from Coptis root, showed greater activity against *M. tuberculosis*, although in certain instances the crude extract was found to be more effective. Whether Coptis root or its alkaloid berberine will have any therapeutic value in the treatment of human tuberculosis remains to be explored. It is known that berberine is highly toxic by parenteral injection; its toxicity by the oral route has not been determined.—*In vitro anti-bacterial activity of some common Chinese herbs on M. tuberculosis, V. F. L. Wang, Chinese M. J., May–June, 1950, 68: 169.*—(*L. Hyde*)

Penicillin and Immunity.—Previous studies indicate that sulfonamide therapy does not affect the development of specific antibodies

but that in acute streptococcal infections penicillin does inhibit the rise in antistreptolysin titers. In this study 44 cases of pneumococcal pneumonia were studied in the acute and convalescent phases for the development of agglutinating and mouse protection antibodies. Of these, 75 per cent developed either one or both of these. The response was not related to the time of treatment whether before or after eighteen hours since the onset of symptoms, presence of bacteremia, or the time-dose treatment schedule used.—*Immunological studies of pneumococcal pneumonia in patients treated with penicillin, W. S. Jordan, Jr., G. F. Badger, & J. H. Dingle, J. Clin. Investigation, February, 1950, 29: 161.*—(*S. Hadley*)

Terramycin in Pneumonia.—Eighteen patients with pneumococcic lobar pneumonia and 7 patients with primary atypical pneumonia were treated with terramycin. The initial dose was 2.0 gm. and was followed by 1.0 gm. every six hours. No serious toxic effects attributable to the terramycin therapy were noted. Symptoms indicative of gastrointestinal irritation, nausea, vomiting, or diarrhea, occurred in 9 of the 25 patients. The response to terramycin therapy was excellent in every case. There were no cases in which the treatment failed. Prompt fall in temperature was observed within 36 hours after the initial dose. Improvement in the acute symptoms often preceded the fall in temperature.—*Terramycin in the treatment of pneumococcic and primary atypical pneumonia, G. W. Melcher, Jr., C. D. Gibson, Jr., H. M. Rose, & Y. Kneeland, Jr., J.A.M.A., August 12, 1950, 143: 1303.*—(*H. Abeles*)

LABORATORY STUDIES

Cytology of Mycobacterium Tuberculosis.—The structure and microchemistry of the Sheard strain of *Mycobacterium tuberculosis* var. *avium* were studied with the electron and light microscopes. The cells were grown on a collodion film deposited on the surface of an agar medium. In these microcultures, the organisms grow initially in a monocellular layer and the cell structure can be seen. For the light microscope, the floated cultures were picked up on a 22 by 40 mm. cover glass instead of a strip of copper screen, and the preparation was placed at a steep angle on blotting or filter paper to dry. The medium was that of Dubos and his co-workers to which was added 20 gm. of agar per liter. The cultures were incubated at 36 to 37°C. in a humid atmosphere and examined after intervals of less than a day to about two weeks. Except when desoxyribonuclease was used, the air-dried preparation was in alcohol. The structure and behavior of the granules were followed in preparations stained with dilute Giemsa's solution. Lipid was demonstrated with Sudan III. Burke's modification of Gram's stain and Ziehl-Neelsen stain were employed. In the test with desoxyribonuclease, the collodion cultures were floated on water at 80°C. for ten minutes, picked up on cover glasses and allowed to dry before being placed in the enzyme or in a control solution. The enzyme solution contained about 5 mg. of the crystalline enzyme per 100 ml. distilled water; after neutral broth was added to raise the pH to about 6.8, the preparations were incubated for thirty minutes or one hour at 45°C. Observations made with the electron microscope showed a cell wall, 230 Å units thick and ductile to an unusual degree. Inside this wall, the cytoplasm is surrounded by a thin cytoplasmic membrane. The cytoplasm and cytoplasmic membrane are highly transparent but not homogeneous, containing numerous rodlike micelles measuring 50 by 300 Å. The cytoplasm encloses 2 other types of bodies, A and C. The A bodies are differentiated into a cortex and a core, the former consisting of chromatin in which desoxyribonucleic acid is associated with both protein and lipid. The nature of the core is unknown; it stains red with Giemsa's solution and is less resistant than the cortex to electronic disintegration. The bodies sometime appear elongated or paired which usually is interpreted as evidence of division. In old cultures this evidence of division is much less frequent; the bodies appear to grow in size so that a single body often occupies an entire cell or the major part of it, a phenomenon also observed in old cultures of *E. coli* and in experi-

mentally aged cultures. It may be said that the entire cell is a nucleus, since the authors conclude that these bodies are nuclear. The existence of lipid, apparently as a part of chromatin is unusual; perhaps some lipid will be found in the chromatin of other bacteria. No evidence was found for the existence of polar bodies distinct from the nuclei. The C bodies are readily observed with the electron microscope but are not easily demonstrable with the light microscope. Since they are unstainable, are highly transparent to the electron beam, exert turgor pressure, and accumulate a solid content that tends to disappear in old cultures, these bodies are to be considered cell-sap vacuoles. The rodlike micelles appear to be distributed in the cytoplasmic membrane and in the cytoplasm. They may be large, complex macromolecules or they may be aggregates of smaller molecules produced by desiccation. They appear to exhibit high surface activity, accumulating around the vacuoles and probably forming the tonoplast (vacuolar membrane). They seem to be integral components of the cytoplasm and, because of their surface activity, accumulate at any interfacial surface. A small amount of benzimidazole added to the medium gradually renders the cells nonacid-fast and gram-negative. Benzimidazole is said to inhibit the synthesis of ribonucleic acid, which explains the alteration in the gram reaction. On the other hand, acid-fastness has always been associated with lipids. Although Sudan III shows that the nuclei and cytoplasm of cells grown in the presence of benzimidazole contain as much lipid material as those of other cells, benzimidazole may inhibit the synthesis of a specific lipid. The Sheard strain of *M. tuberculosis* has cytoplasm that is practically unstainable with the dyes used and is highly transparent to the electron beam; it is surrounded by slime which is stainable and opaque to the electron beam. The slime does not give the lipid test with either Sudan III or Sudan black B, but stains red with aged Loeffler's methylene blue, a property of volutin which is chiefly ribonucleic acid. This substance usually is present in the cytoplasm and is the cause of its deep staining in bacteria. In this strain ribonucleic acid in some combination may be extraprotoplasmic or formed in the protoplasm and eliminated at the cell surface. —*The cytology of an avian strain of Mycobacterium tuberculosis studied with the electron and light microscopes, G. Knaysi, J. Hillier, & C. Fabricant, J. Bact., October 1950, 60: 423.*—(*F. G. Petrik*)

Laryngeal Swab.—The results of examining for tubercle bacilli the specimens obtained by gastric lavage and laryngeal swab were compared in 56 cases of pulmonary tuberculosis; each patient had two consecutive negative sputum concentrates. The gastric specimen was examined by the concentration method and cultured only if the latter proved negative. In all, 27 patients had positive bacteriologic results. In 48 of the 56 patients the results were concordant with the 2 methods; 19 being positive and 29 negative. Four patients were positive with gastric lavage alone, 4 other patients, with laryngeal cultures only. Since each method yielded false negative results and the use of both increased the number of positive findings, the disadvantages of gastric lavage are: (*1*) the patient has to be fasting; (*2*) aspiration is difficult in some patients and others refuse to have the procedure performed; (*3*) tubercle bacillus can be destroyed by gastric juice if laboratory examination of the specimen is delayed too long; and (*4*) there is risk of contamination. Advantages of the laryngeal swab are: (*1*) it is accepted by patients; (*2*) it can be performed at any time during the day; (*3*) it is less time consuming and therefore more suitable for serial examinations; and (*4*) specimens rarely are contaminated.—*La recherche du bacille tuberculeux par la culture du prélèvement laryngé. Comparison avec les résultats des examens sur lames et les cultures du liquide de lavage gastrique, G. E. Renoux & A. Français, Presse méd., April 8, 1950: 392.*—(*V. Leites*)

Hemagglutination Test for Tuberculosis.—Specific agglutination of sheep or human red blood cells sensitized with Old Tuberculin was tested in 580 samples of serum. Of 220 tests of sera from normal and nontuberculous patients,

only 8 showed any agglutination of cells and these in titers of 1:4 or less. Of sera from 157 patients with active tuberculosis, 92 per cent showed agglutination titers of 1:8 to 1:512 with a mean of 1:32. Tests of the sera of 50 patients with arrested disease revealed 25 with no antibody while the others tested 1:8 or higher.—*The practical application of a hemagglutination reaction in pulmonary tuberculosis, S. Rothbard, A. Dooneief, & K. Hite, J. Clin. Investigation, June, 1950, 29: 842.*—(*S. Hadley*)

Absorption of Aerosols.—Using a specially designed apparatus, the authors measured with great care the sodium *p*-aminohippurate delivered in aerosol to 5 subjects. They determined the amount delivered to the subject, the amount expired by the subject, as well as the amount that accumulated in the valves, mouth, and saliva. As a check they also measured the amount excreted in the urine over a twelve-hour period. They were able to account for 93 per cent of the material delivered and found a good correlation between the two methods used for determining the amount finally absorbed by the subjects. It was found that approximately 47 per cent (41 to 52.5 per cent) of the quantity inspired was absorbed. In addition it was demonstrated that very little was taken up from the mouth. The measurement of the substance excreted in the urine is the more easy of the two methods. The authors suggest that, by incorporating sodium *p*-aminohippurate in a solution to be nebulized, the method could be easily modified for the study of the pulmonary retention of other substances.—*The pulmonary retention of aerosol: A quantitative method of measurement using sodium para-aminohippurate, W. Franklin, C. Denton, & F. Lowell, J. Clin. Investigation, September, 1950, 29: 1177.*—(*S. Hadley*)

Beryllium Granulomata.—By the intratracheal injection of powdered beryllium oxide suspended in saline or skim milk, multiple small granulomata were caused to develop in rats. These were chiefly of the foreign-body type composed of small mononuclear cells with an occasional multinuclear cell and infiltration of interstitial tissues. This lesion is believed to be related specifically to beryllium oxide. Its occurrence in the lungs of rats is associated with the rate of solution of the particles, this rate being determined by the size of the particle and the solubility of beryllium. Granulomata occur when particulate dust persists in aggregations to form a continuing irritant focus.—*Beryllium granulomata in the lungs of rats, T. A. L. Davies & H. E. Harding, Brit. J. Indust. Med., April, 1950, 7: 70.*—(*L. Levin*)

Aluminium and Silicosis Production.—Rats were dusted experimentally with quartz alone or with quartz plus aluminium in a chamber devised for the purpose. A distinct difference was observed in the lungs of the 2 groups of animals. Those animals dusted with quartz alone presented nodular reticulinosis from approximately the two hundredth day of dusting and fully developed collagenous silicosis from approximately the three hundredth day. At 200 days the rats dusted with quartz plus aluminium had almost no reticulinosis and had only slight reticulinosis at 300 days. The impression gained is that the presence of 2 per cent aluminium has slowed the pathogenic action of quartz by approximately 200 days. Just as much quartz was found in the lungs of the aluminium-plus-quartz group as in the lungs of animals dusted with quartz alone.—*Effect of aluminium on the silicosis-producing action of inhaled quartz, E. J. King, B. M. Wright, S. C. Ray, & C. V. Harrison, Brit. J. Indust. Med., January, 1950, 7: 27.*—(*L. Levin*)

Survival after Decompression.—The effects of 16 chemical compounds on survival to explosive decompression at a pressure of 105 mm. Hg. (equivalent to 3 per cent oxygen at sea level pressure) were measured with mice, this pressure in the case of the mouse being equivalent to complete anoxia. Substances prolonging survival were the alcohols, glucose, morphine, posterior pituitary extract, epinephrine, iodo-

acetic acid, chloralose, and desoxycorticosterone. Those shortening survival were ephedrine, insulin, histamine, lobeline, ergotoxine, and prostigmine (Authors' summary). —*Chemical agents influencing survival to explosive anoxia, F. W. Stemler, J. E. Stiebers, & W. A. Hiestand, Am. J. Physiol., November 1, 1950, 163: 400.*—(*G. C. Leiner*)

Lung Volume.—Measurements of changes of total lung volume during respiration were carried out with a body-plethysmograph on rabbits and cats narcotized with methane. Lack of oxygen (5 to 8 per cent oxygen) regularly increased the lung volume; carbon dioxide (2 to 10 per cent) in the inspired air had no such effect, in spite of increased ventilation. Lack of oxygen mainly increased the number of respirations; carbon dioxide, mainly the respiratory volume. There was no quantitative correlation between the increase of the total lung volume and the increase of the rate, the increase of the volume of respiration (total air), and the increase of the respiratory minute volume. The factor which influences the total lung volume is the lack of oxygen. Lung volume increases as the oxygen content of the inspired air decreases (Authors' summary). —*Influence of O_2 content of inspired air on total lung volume, E. Peyser, A. Sass-Kortsak, & F. Verzar, Am. J. Physiol., October 1, 1950, 163: 111.*—(*G. C. Leiner*)

Oxygen and Erythropoiesis.—It has long been known that decreased oxygen tension stimulates erythrocyte formation. The authors' study was for the purpose of corroborating animal data which showed that high oxygen concentration resulted in anemia. Patients with sickle cell, pernicious, and congenital hemolytic anemias were studied primarily because the rate of red blood cell turnover in them is rapid. Oxygen concentrations of 50 per cent or more in the inspired air administered for a week or more resulted in a dramatic decrease in reticulocytes and a fall of the red blood cell count in congenital hemolytic anemia. The counts returned to normal when oxygen was discontinued. In pernicious anemia, the response to vitamin B12 was submaximal during oxygen therapy. And in the normal patients the rate of appearance of intravenous radioactive iron was slower during oxygen therapy than after. In all cases the pH and the carbon dioxide content of the blood did not change. The implications in prolonged oxygen therapy may be of interest. —*The role of oxygen in the regulation of erythropoiesis: Depression of the rate of delivery of new red cells to the blood by high concentrations of inspired oxygen, C. Moore, R. Dubach, V. Minnich, & M. Grinstein, J. Clin. Investigation, November, 1949, 28: 1544.*—(*S. Hadley*)

Vital Capacity Tests.—Repeated attempts have been made to establish vital capacity tests as a measure of over-all pulmonary function. The present scheme is a more rational application of the vital capacity measurement. The ventilatory capacity (maximum breathing capacity) was determined with a spirometer without valves or a carbon dioxide absorber, the results comparing well with other investigators' data. These measurements were correlated with the vital capacity and the maximum expiratory pressure measured as the pressure developed in an aneroid manometer by deep expiration. Also the influence of increased air-flow resistance on ventilatory capacity was determined by inserting plastic tubes of varying diameters into the spirometer system. The ventilatory capacity was found to correlate weakly with the vital capacity but experimental reduction in vital capacity reduced the ventilation capacity proportionately, leaving the ventilation capacity per liter of vital capacity (the capacity ratio) unchanged. There was no correlation with maximum expiratory pressure. The introduction of increased resistance to air flow, however, depressed the ventilation capacity and the capacity ratio but left the vital capacity unchanged. These results serve to demonstrate the various factors that influence ventilatory capacity. The first is the size of the bellow. It is this that the vital capacity measures, as seen when the vital capacity is reduced without change in the capacity ratio.

Second and third are the influence of excessive resistance and impaired motive power. These are demonstrated when there is a decrease in capacity ratio with or without change in vital capacity. The present studies indicate that unless there is severe muscular impairment the effects of impaired motive power are small. On the other hand, it is shown that air-flow resistance in the respiratory passages and resistance of the lung and thorax are powerful factors in reducing ventilatory capacity and do so without influencing the vital capacity.—*Ventilatory function tests: II. Factors affecting the voluntary ventilation capacity, H. Matheson, S. Spies, J. Gray, & D. Barnum, J. Clin. Investigation, June, 1950, 29: 82.—(S. Hadley)*

PUBLIC HEALTH AND EPIDEMIOLOGY

Routine Admission Studies.—Five routine procedures were carried out on 951 patients admitted to a private diagnostic clinic: (*1*) complete blood count, (*2*) hemoglobin and sedimentation rate, (*3*) urinalysis, (*4*) blood serology, and (*5*) stereo-photoroentgenogram of the chest. Obstetrical patients and those with specific chest complaints were excluded from a study of the results. There were 336 men and 615 women from 12 to 82 years of age with an average age of 41 years. Significant pulmonary disease was found in 21 patients (2.2 per cent), 7 of whom (0.7 per cent) had minimal active tuberculosis. Syphilis was diagnosed in 8 instances (0.84 per cent). A total of 159 patients (16.8 per cent) had sedimentation rates higher than normal; 70 (7.4 per cent) had a hemoglobin concentration below 75 per cent; 124 (13.1 per cent) showed abnormal urinary findings, diabetes mellitus being diagnosed in 5 instances (0.5 per cent). It was concluded that routine photoroentgenographic chest examination reveals at least as much pathology as is demonstrated by the laboratory procedures.—*Detection of pulmonary tuberculosis: Comparative value of routine radiologic examinations and routine laboratory procedures, H. D. Peabody, Jr. & R. H. Sundberg, California Med., June, 1950, 72: 461.—(E. A. Rouff)*

Tuberculosis Control in Italy.—In 1887 the tuberculosis death rate in Italy was 211 per 100,000 in a population of 29 million inhabitants. By 1914 the rate was only 145 per 100,000 in a 35 million population. World War I brought about a sharp increase, and by 1918 the tuberculosis death rate had risen to 209 per 100,000. As postwar conditions improved, the former trend reasserted itself. By 1921 the rate was 142 and by 1939 it was 76 per 100,000 in a 44 million population. The picture changed with the advent of World War II and by 1942 the rate was 110 per 100,000. By 1946 the rate had dropped again to 84 per 100,000 for a 45 million population. As regards morbidity, available data show approximately 12 cases for each death. In the decade immediately preceding World War II, the average number of tuberculous patients was between 300,000 and 400,000, this figure decreasing almost parallel with the number of deaths. Tuberculosis control in Italy reflects to a large degree the ideas and efforts of Prof. E. Morelli. A provincial body in each of the 91 provinces controls or conducts all of the tuberculosis work. Together these bodies operate 497 dispensaries and a number of sanatoriums. The Social Security Institute, which carries tuberculosis insurance, operates independently more than 50 sanatoriums. The National Red Cross also has some tuberculosis sanatoriums and hospitals. Most of the largest general hospitals include tuberculosis sections. Postgraduate courses in tuberculosis are offered at the principal medical schools. Courses in tuberculosis nursing are given at the large sanatoriums. Surgical clinics for tuberculosis patients are available at both sanatoriums and university centers. A traveling roentgenographic unit provides a diagnostic service similar to that furnished by dispensaries. The number of registered physicians in Italy was 33,069 in 1939 and has practically doubled since then. The 47,139 beds available for tuberculous patients in 1939 reached 51,419 in 1946, i.e., 1,126 beds per million inhabitants. This is admittedly inadequate. In brief, the advances in 50 years of tuberculosis control are as follows: tuberculosis mortality has been

cut by more than half; morbidity has dropped sensibly; a tuberculosis consciousness among the people is being developed; and preventive measures, in spite of obvious deficiencies, are constantly improving. Continuance and extension of the campaign is essential as tuberculosis is still the chief cause of death among communicable diseases, and antituberculosis progress lags far behind that made against other infectious diseases. Among the 6 largest cities tuberculosis has given ground only in Turin since 1939. In the other 5 cities, the number of tuberculosis deaths rose 12 to 72 per cent between 1939 and 1945.—*Consideraciones sobre 50 años de lucha antituberculosa en Italia, M. Tomassini, Rev. Tuberc., July-December, 1949, 9: 180.*—(*A. A. Moll*)

Tuberculosis in Yugoslavian Army.—Although the incidence of tuberculosis is decreasing in Yugoslavia, this disease remains the most common illness in the army. A recent survey showed that 1.54 per cent of trained soldiers had active tuberculosis and 7.4 per cent had inactive disease. Only 0.91 per cent of draftees had active tuberculosis; 6.05 per cent had inactive disease. Only 15.3 per cent of all soldiers were tuberculin negative. The location of the tuberculous lesions in the army patients differed among the various ranks: 72 per cent of the commissioned patients had tuberculosis of the lungs, 14 per cent had serosal lesions; 64 per cent of noncommissioned officer patients had pulmonary lesions, 24 per cent had serosal lesions; 48 per cent of the privates who were patients had pulmonary lesions and 40 per cent had serosal tuberculosis. Tuberculosis of a serous membrane is the "private's illness." At the time of hospitalization, 21 per cent of the tuberculosis patients were infectious, and at discharge, after an average of 64 days of treatment, 38 per cent were still bacteriologically positive. Of all the patients, 39 per cent were considered suitable for collapse therapy. Pneumothorax was used in 82 per cent of this group, pneumonolysis in 8 per cent, thoracoplasty in 6 per cent, and other procedures in 4 per cent. At present, all tuberculin-negative soldiers receive BCG vaccination.—*A survey of the tuberculosis control in the Yugoslavian Army in 1948 (Yugoslavian), S. Jezdimir, Tuberkuloza, December, 1949, 1: 413.*—(*J. Ilavsky*)

Evaluation of Tuberculosis Allergy.—Among 26,000 patients seen during a 15-year period, mostly in a tuberculosis dispensary at Lima, 50,000 tuberculin tests and 40,000 fluoroscopic examinations were made. It was confirmed that tuberculous allergy is different from other allergies and is of an acquired character. Tuberculin diagnosis remains a true measurement of the epidemiologic situation. A positive reaction to tuberculin protein may be the only sign revealing the status of a tuberculous infection in a receptive individual. A standardized technique enhances the value of such surveys but as yet there is no perfect test. In practice, the tuberculin patch gives a high yield of positive results but it is lower than that obtained with the skin test, using more than 1 mg. of tuberculin. In this series, the difference in favor of the latter ran as high as 16.3 per cent. In groups of children, a greater use of Vollmer's method seems desirable.—*Tisioalergometria, E. del Río R., Rev. Tuberc., July-December, 1949, 9: 262.*—(*A. A. Moll*)

Diagnostic BCG Skin Test.—The diagnostic value of the skin-puncture test with BCG was studied in 1,121 individuals divided into one group of 423 school children six to fourteen years of age, and a second group of 698 university students. In both groups, photoroentgenograms of the chest were made. In the first group, a single-puncture BCG test and a von Pirquet test with Old Tuberculin were performed simultaneously. If the latter was negative, a Mantoux test with OT, 10 mg., was performed four days later. Each child was examined at four, eight, twenty-one, and forty-five days to determine if a BCG nodule appeared. The students in the second group all gave negative results with the von Pirquet test and with the Mantoux test, using OT, 1 mg. In these a Mantoux test with OT, 10 mg., and a double-puncture test with BCG

were performed simultaneously. Various combinations of results were observed in these individuals: (*1*) both 10 mg. Mantoux and BCG negative, the noninfected group; (*2*) 10 mg. Mantoux negative and prompt BCG response, a group with infratuberculinic allergy; (*3*) 10 mg. Mantoux positive and BCG negative early, a group possibly with a nonspecific tuberculin reaction and a doubtful BCG response. An analysis of the results led to the conclusions that: (*1*) The skin test with BCG is not advocated as a tool for investigating allergy, in children at least, because of the intense reaction which it may produce in those reacting to the von Pirquet test. (*2*) This BCG test seems indicated to supplement the Mantoux tests at 1 and 10 mg. concentrations because it allows the recognition of all those who would react to tuberculin tests and, in addition, detects those with an infratuberculinic state of allergy. (*3*) The BCG skin test shows that all nodular reactions to the intradermal tuberculin tests must be interpreted as positive regardless of their diameter on the third or fourth day. Interpreting as nonspecific all those smaller than 10 mm. in diameter would result in classifying as "not infected" a good percentage of hypergic persons. (*4*) An advantage of the BCG skin reaction is the concurrent production of some vaccination or anamnestic reaction to increase the protection against clinical infection.—*Valor diagnóstico de la cutipuntura con B.C.G., F.D. Gómez, A. Piaggio, & C. Epifanio, Hoja Tisiol., June, 1950, 10: 121.*—(*F. Pérez-Pina*)

BCG Vaccination of Nurses.—The results of BCG vaccination in the National School of Nursing at Lima justify its extended use. In view of the high percentage of changes in the tuberculin reaction between the first and the second school years, BCG vaccination should be required on admission to schools of nursing and medicine. A 0.10 mg. dose seems to be adequate. Revaccination should be carried out at least once when annual control examinations show the return of anergy. In all cases of hyperergy a roentgenographic examination is essential. Isolation should be enforced both immediately before and after vaccination whenever feasible.—*Encuesta epidemiológica y B. C. G. en la Escuela Nacional de Enfermeras, E. Williams, Rev. Tuberc., July–December, 1949, 9: 261.*—(*A. A. Moll*)

Graphite Pneumoconiosis.—A study of 415 graphite workers revealed 12 cases of pulmonary tuberculosis and 24 of pneumoconiosis. Of the latter 24, 16 had reticulation, 7 had nodular pneumoconiosis, and one had massive pneumoconiosis. The disease occurred more frequently among miners and millers than among electrode workers. Prognosis is generally favorable and tuberculosis is less frequent than in typical silicosis. Since specific lesions are more frequent among the young workers and do not increase among the older ones, it is possible that inhaling graphite dust does not aggravate the progress of tuberculous lesions but facilitates fibrosclerotic development.—*Graphite pneumoconiosis, L. Parmeggiani, Brit. J. Indust. Med., January, 1950, 7: 42.*—(*L. Levin*)

Effect of Long Exposure to Sulfur Dioxide.—This study was motivated by the often repeated opinion that long-contir..ed exposure to fumes of sulfur dioxide was a contributory cause of tuberculosis, bronchitis, and other chronic chest disease. Controls and contacts were compared as to age, weight, blood pressure, vital capacity, and radiographic findings. Of significance is the fact that 122 contacts showed a better mean vital capacity than 129 controls and that there was no evidence that their health was suffering as a result of exposure to sulfur dioxide. No cases of active tuberculosis were found. The contacts had been exposed for periods of time varying from one to nineteen years in a daily concentration of sulfur dioxide from none to 25 p.p.m.—*Possible long term effects of exposure to sulphur dioxide, A. Anderson, Brit. J. Indust. Med., April, 1950, 7: 82.*—(*L. Levin*)

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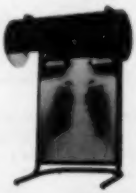

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With reluctance, therefore, we are forced to announce an increase in the subscription rate from $8.00 to $10.00.

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NATIONAL TUBERCULOSIS ASSOCIATION

Annual Meeting **May 15–18, 1951**

Cincinnati, Ohio

The annual meeting of the National Tuberculosis Association will be held in Cincinnati, Ohio, May 15-18, 1951. The Netherland Plaza Hotel will be headquarters.

Some 1500 rooms have been promised by the hotels listed below for the accommodation of those attending the meeting. Arrange to share a double room if possible.

Application for room reservations should be made directly with the hotel of your choice.

Hotel	*Address*	*Single*	*Double*
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See March issue of NTA Bulletin for preliminary program.

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